

## CARBOXYLIC DERIVATES

### Field of the invention

The present invention relates to certain novel 3-(amino-oxo(alkyl, alkyloxy and  
5 alkylthio)phenyl) propanoic and propenoic acid derivatives, to processes for preparing  
such compounds, to their utility in treating clinical conditions including lipid disorders  
(dyslipidemias) whether or not associated with insulin resistance and other manifestations  
of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical  
compositions containing them.

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### Background of the invention

The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of  
manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly  
type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia  
15 observed as deranged lipoprotein levels typically characterised by elevated VLDL (very  
low density lipoproteins), small dense LDL particles and reduced HDL (high density  
lipoprotein) concentrations and reduced fibrinolysis.

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Recent epidemiological research has documented that individuals with insulin resistance  
run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering  
from myocardial infarction and stroke. In type 2 diabetes mellitus atherosclerosis related  
conditions cause up to 80% of all deaths.

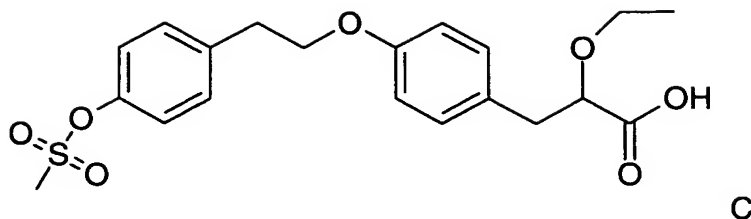
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In clinical medicine there is awareness of the need to increase the insulin sensitivity in  
patients with the metabolic syndrome and thus to correct the dyslipidaemia which is  
considered to cause the accelerated progress of atherosclerosis. However, currently this is  
not a universally accepted diagnosis with well-defined pharmacotherapeutic indications.

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The S-enantiomer of the compound of formula C below

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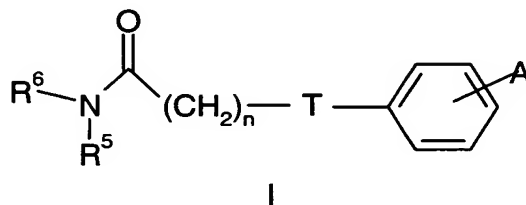
2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, is disclosed in PCT Publication Number WO99/62872. This compound is reported to be a modulator of peroxisome proliferator-activated receptors (PPAR, for a review of the PPARs see T. M. Willson et al, J Med Chem 2000, Vol 43, 527) and has combined  
 5 PPAR $\alpha$ /PPAR $\gamma$  agonist activity (Structure, 2001, Vol 9, 699, P. Cronet et al). This compound is effective in treating conditions associated with insulin resistance.

Surprisingly a series of compounds has now been found which are selective PPAR $\alpha$   
 10 modulators.

### Description of the invention

The present invention provides a compound of formula I

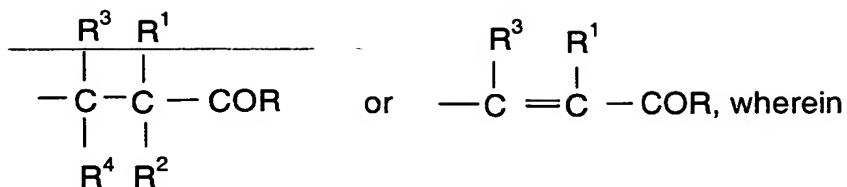
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as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof

20 wherein

A is situated in the ortho, meta or para position and represents



R is hydrogen;

-OR<sup>a</sup>, wherein R<sup>a</sup> represents hydrogen, alkyl, aryl or alkylaryl;

5 -NR<sup>a</sup>R<sup>b</sup>, wherein R<sup>a</sup> and R<sup>b</sup> are the same or different and R<sup>a</sup> is as defined above and R<sup>b</sup> represents hydrogen, alkyl, aryl, alkylaryl, cyano, -OH, -Oalkyl, -Oaryl, -Oalkylaryl, -COR<sup>c</sup> or -SO<sub>2</sub>R<sup>d</sup>, wherein R<sup>c</sup> represents hydrogen, alkyl, aryl or alkylaryl and R<sup>d</sup> represents alkyl, aryl or alkylaryl;

10 R<sup>1</sup> is alkyl, aryl, alkenyl, alkynyl, or when A is  $\begin{array}{c} \text{R}^3 \quad \text{R}^1 \\ | \quad | \\ -\text{C}-\text{C}-\text{COR} \\ | \quad | \\ \text{R}^4 \quad \text{R}^2 \end{array}$  R<sup>1</sup> can also be cyano;

-OR<sup>e</sup>, wherein R<sup>e</sup> is alkyl, acyl, aryl or alkylaryl;

-O-[CH<sub>2</sub>]<sub>m</sub>-OR<sup>f</sup>, wherein R<sup>f</sup> represents hydrogen, alkyl, acyl, aryl or alkylaryl and m represents an integer 1-8;

15 -OCONR<sup>a</sup>R<sup>c</sup>, wherein R<sup>a</sup> and R<sup>c</sup> are as defined above;

-SR<sup>d</sup>, wherein R<sup>d</sup> is as defined above;

-SO<sub>2</sub>NR<sup>a</sup>R<sup>f</sup>, wherein R<sup>f</sup> and R<sup>a</sup> are as defined above;

-SO<sub>2</sub>OR<sup>a</sup>, wherein R<sup>a</sup> is as defined above;

-COOR<sup>d</sup>, wherein R<sup>d</sup> is as defined above;

20 R<sup>2</sup> is hydrogen, halogen, alkyl, aryl, or alkylaryl,

R<sup>3</sup> and R<sup>4</sup> are the same or different and each represents hydrogen, alkyl, aryl, or alkylaryl;

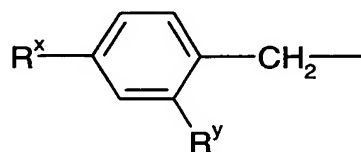
T represents O, S or a single bond;

n represents 1, 2, 3 or 4;

- 5  $R^5$  and  $R^6$  are independently selected substituents, comprising C, H, N, O, S, Se, P or halogen atoms, which give compounds of the General Formula I a molecular weight < 650;

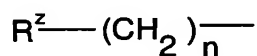
with a first proviso that

- 10 when A is  $\text{CH}_2\text{CH}(\text{OC}_2\text{H}_5)\text{COOC}_2\text{H}_5$  or  $\text{CH}_2\text{CH}(\text{OC}_2\text{H}_5)\text{COOH}$ ; T is O; n is 1 and  $R^5$  represents a  $\text{C}_{2-4}$ alkyl group then  $R^6$  does not represent a group of formula



wherein  $R^x$  represents chloro, trifluoromethyl or trifluoromethoxy,  $R^y$  represents H or fluoro;

- 15 and a second proviso that when A is  $\text{CH}_2\text{CH}(\text{OC}_2\text{H}_5)\text{COOC}_2\text{H}_5$  or  $\text{CH}_2\text{CH}(\text{OC}_2\text{H}_5)\text{COOH}$ ; T is O; n is 1 and  $R^5$  represents hexyl or heptyl then  $R^6$  does not represent a group of formula



wherein  $R^z$  represents phenyl, 2,4-difluorophenyl or cyclohexyl, and n is 1 or 2;

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provided that the compound of formula I is not:

(2S)-4-[2-[[2-[[[(2,6-dichlorophenyl)methyl]thio]ethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

- 25 (2S)-4-[2-[butyl(1-phenylethyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

(2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[2-(3-pyridinyl)ethyl]amino]ethoxy]- benzenepropanoic acid;

(2S)- $\alpha$ -methyl-4-[2-oxo-2-[[2-(4-

- phenoxyphenyl)ethyl]amino]ethoxy]- $\alpha$ -phenoxy- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-[(1-methyl-3-phenylpropyl)amino]-2-oxoethoxy]- benzenepropanoic acid;
- 5 (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[4-[4-(trifluoromethyl)phenyl]-1-piperazinyl]ethoxy]- benzenepropanoic acid;
- (2S)-4-[2-[[2-(4-bromophenyl)ethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 10 (2S)-4-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-[[2-[ethyl(3-methylphenyl)amino]ethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 15  $\alpha$ -methoxy- $\alpha$ -methyl-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-[(3-methylbutyl)amino]-2-oxoethoxy]- benzenepropanoic acid;
- (2S)-4-[2-[4-(diphenylmethyl)-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 20 (2S)-4-[2-(heptylamino)-2-oxoethoxy]- $\alpha$ -methoxy- $\alpha$ -methyl- benzenepropanoic acid;
- 4-[2-[4-(2-fluorophenyl)-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy-, benzenepropanoic acid;
- (2S)-4-[2-[4-(4-chlorobenzoyl)-1-piperidinyl]-2-oxoethoxy]- $\alpha$ -methoxy-, benzenepropanoic acid;
- 25 (2S)-4-[2-[4-(4-chlorobenzoyl)-1-piperidinyl]-2-oxoethoxy]- $\alpha$ -methoxy-, benzenepropanoic acid;
- (2S)-4-[2-[ethyl[(3-methylphenyl)methyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[(4-phenoxyphenyl)amino]ethoxy]- benzenepropanoic acid;
- 30 (2S)- $\alpha$ -methoxy-4-[2-[(1-methylhexyl)amino]-2-

- oxoethoxy]- benzenepropanoic acid;
- (2S)-4-[2-[[[1,1'-biphenyl]-4-ylmethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 5 3-[2-[[[cis-4-(1,1-dimethylethyl)cyclohexyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-[4-(3-chlorophenyl)-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-[methyl[(1S)-1-phenylethyl]amino]-2-oxoethoxy]- benzenepropanoic acid;
- 10 (2S)- $\alpha$ -methoxy-4-[2-[4-(4-methylphenyl)-1-piperazinyl]-2-oxoethoxy]- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-[[[3-(methylphenylamino)propyl]amino]-2-oxoethoxy]- benzenepropanoic acid;
- (2S)-4-[2-(cyclobutylamino)-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 15 (2S)- $\alpha$ -methyl-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- $\alpha$ -[4-(trifluoromethoxy)phenoxy]- benzenepropanoic acid;
- (2S)-4-[2-(heptylamino)-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-[4-(4-fluorophenyl)-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 20 (2S)- $\alpha$ -methoxy-4-[2-[[[1S)-1-(1-naphthalenyl)ethyl]amino]-2-oxoethoxy]- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[[1R)-1-phenylethyl](phenylmethyl)amino]ethoxy]- benzenepropanoic acid;
- 25 (2S)-4-[2-[[[3,3-diphenylpropyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-[[[trans-4-(1,1-dimethylethyl)cyclohexyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)- $\alpha$ -methyl-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- $\alpha$ -phenoxy-, ethyl ester- benzenepropanoic acid;
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- (2S)-4-[2-[(2,2,3,3,4,4,4-heptafluorobutyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-(3,4-dihydro-2(1H)-isoquinolinyl)-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 5 (2S)-3-[2-[[2-(4-ethylphenyl)ethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-[(1-naphthalenylmethyl)amino]-2-oxoethoxy]- benzenepropanoic acid;
- 10 (2S)-4-[2-[[4-(4-chlorophenyl)phenylmethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[2-(2-pyridinyl)ethyl]amino]ethoxy]- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[1-(1S)-1-phenylethyl]amino]ethoxy]- benzenepropanoic acid;
- 15 (2S)-4-[2-(cyclopentylamino)-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 20 4-[2-[cyclohexyl[2-(4-ethylphenyl)ethyl]amino]-2-oxoethoxy]- $\alpha$ -ethoxy- benzenepropanoic acid;
- (2S)-4-[2-[(1,3-benzodioxol-5-ylmethyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- D-Phenylalanine, N-[[4-[(2S)-2-carboxy-2-methoxyethyl]phenoxy]acetyl]-,  $\alpha$ -methyl ester;
- 25 (2S)-4-[2-[4-[(4-fluorophenyl)methyl]-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- $\alpha$ -methoxy-3-[2-oxo-2-[(4-phenoxyphenyl)amino]ethoxy]- benzenepropanoic acid;
- 30 (2S)- $\alpha$ -methoxy-4-[2-[(1-methylbutyl)amino]-2-oxoethoxy]- benzenepropanoic acid;

- (2S)- $\alpha$ -methoxy-4-[2-[methyl(1-naphthalenylmethyl)amino]-2-oxoethoxy]-benzenepropanoic acid;
- (2S)-3-[2-[[trans-4-(1,1-dimethylethyl)cyclohexyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- 5 (2S)-4-[2-[4-[(4-chlorophenyl)methyl]-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- (2S)-4-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- 10 (2S)-4-[2-[ethyl[(2-fluorophenyl)methyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-[[2-(4-methoxyphenoxy)ethyl]amino]-2-oxoethoxy]-benzenepropanoic acid;
- (2S)-4-[2-[(1,3-dimethylbutyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- 15 (2S)- $\alpha$ -(4-fluorophenoxy)- $\alpha$ -methyl-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]-benzenepropanoic acid;
- (2S)-4-[2-[(3,3-dimethylbutyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- (2S)-4-[2-[4-(4-chlorophenyl)-3-methyl-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- 20 (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[2-(4-phenylethyl)amino]ethoxy]-benzenepropanoic acid;
- (2S)-4-[2-[4-(4-acetylphenyl)-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- 25 (2S)-4-[2-[(3-ethoxy-3-oxopropyl)(phenylmethyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- (2S)-4-[2-[[cis-4-(1,1-dimethylethyl)cyclohexyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy-benzenepropanoic acid;
- (2S)- $\alpha$ -ethyl-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- $\alpha$ -phenoxy-benzenepropanoic acid;
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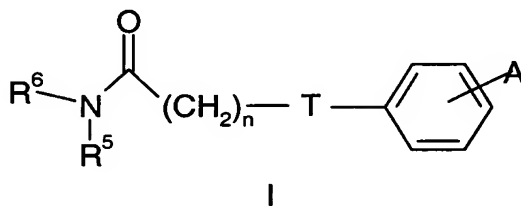
(2S)-4-[2-(hexylamino)-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

(2S)- $\alpha$ -methoxy-4-[2-oxo-2-[(2-phenylethyl)(phenylmethyl)amino]ethoxy]- benzenepropanoic acid;

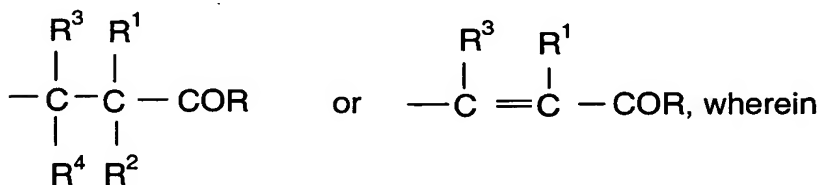
or

5 (2S)-4-[2-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid.

According to another aspect the invention provides for a compound of formula I



10 as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof wherein A is situated in the ortho, meta or para position and represents



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R is hydrogen;

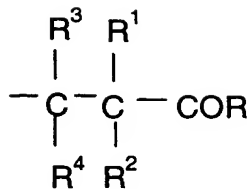
-OR<sup>a</sup>, wherein R<sup>a</sup> represents hydrogen, alkyl, aryl or alkylaryl;

-NR<sup>a</sup>R<sup>b</sup>, wherein R<sup>a</sup> and R<sup>b</sup> are the same or different and R<sup>a</sup> is as defined above

and R<sup>b</sup> represents hydrogen, alkyl, aryl, alkylaryl, cyano, -OH, -Oalkyl, -Oaryl, -

20

Oalkylaryl, -COR<sup>c</sup> or -SO<sub>2</sub>R<sup>d</sup>, wherein R<sup>c</sup> represents hydrogen, alkyl, aryl or alkylaryl and R<sup>d</sup> represents alkyl, aryl or alkylaryl;



$R^1$  is alkyl, aryl, alkenyl, alkynyl, or when A is cyano;

$-OR^e$ , wherein  $R^e$  is alkyl, acyl, aryl or alkylaryl;

$-O-[CH_2]_m-OR^f$ , wherein  $R^f$  represents hydrogen, alkyl, acyl, aryl or alkylaryl  
and m represents an integer 1-8;

$-OCONR^aR^c$ , wherein  $R^a$  and  $R^c$  are as defined above;

$-SR^d$ , wherein  $R^d$  is as defined above;

$-SO_2NR^aR^f$ , wherein  $R^f$  and  $R^a$  are as defined above;

$-SO_2OR^a$ , wherein  $R^a$  is as defined above;

$-COOR^d$ , wherein  $R^d$  is as defined above;

$R^2$  is hydrogen, halogen, alkyl, aryl, or alkylaryl,

$R^3$  and  $R^4$  are the same or different and each represents hydrogen, alkyl, aryl, or alkylaryl;

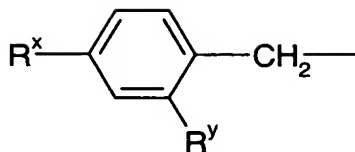
T represents O, S or a single bond;

n represents 1, 2, 3 or 4;

$R^5$  and  $R^6$  are independently selected substituents, comprising C, H, N, O, S, Se, P or halogen atoms, which give compounds of the General Formula I a molecular weight < 650;

with a first proviso that

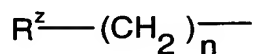
when A is  $CH_2CH(OC_2H_5)COOC_2H_5$  or  $CH_2CH(OC_2H_5)COOH$ ; T is O; n is 1 and  $R^5$  represents a  $C_{2-4}$ alkyl group then  $R^6$  does not represent a group of formula



wherein  $R^x$  represents chloro, trifluoromethyl or trifluoromethoxy,  $R^y$  represents H or fluoro;

and a second proviso that when A is  $CH_2CH(OC_2H_5)COOC_2H_5$  or  $CH_2CH(OC_2H_5)COOH$

5 ; T is O; n is 1 and  $R^5$  represents hexyl or heptyl then  $R^6$  does not represent a group of formula



wherein  $R^z$  represents phenyl, 2,4-difluorophenyl or cyclohexyl, and n is 1 or 2;

10 provided that the compound of formula I is not:

(2S)-4-[2-[[2-[(2,6-dichlorophenyl)methyl]thio]ethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

(2S)-4-[2-[butyl(1-phenylethyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

15 (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[2-(3-pyridinyl)ethyl]amino]ethoxy]- benzenepropanoic acid;

(2S)- $\alpha$ -methyl-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- $\alpha$ -phenoxy- benzenepropanoic acid;

20 (2S)- $\alpha$ -methoxy-4-[2-[(1-methyl-3-phenylpropyl)amino]-2-oxoethoxy]- benzenepropanoic acid;

(2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- benzenepropanoic acid;

(2S)- $\alpha$ -methoxy-4-[2-oxo-2-[4-[4-(trifluoromethyl)phenyl]-1-piperazinyl]ethoxy]- benzenepropanoic acid;

25 (2S)-4-[2-[[2-(4-bromophenyl)ethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

(2S)-4-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

(2S)-4-[2-[[2-[ethyl(3-methylphenyl)amino]ethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

$\alpha$ -methoxy- $\alpha$ -methyl-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- benzenepropanoic acid;

5 (2S)- $\alpha$ -methoxy-4-[2-[(3-methylbutyl)amino]-2-oxoethoxy]- benzenepropanoic acid;

(2S)-4-[2-[4-(diphenylmethyl)-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

10 (2S)-4-[2-(heptylamino)-2-oxoethoxy]- $\alpha$ -methoxy- $\alpha$ -methyl- benzenepropanoic acid;

4-[2-[4-(2-fluorophenyl)-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy-, benzenepropanoic acid;

(2S)-4-[2-[4-(4-chlorobenzoyl)-1-piperidinyl]-2-oxoethoxy]- $\alpha$ -methoxy-, benzenepropanoic acid;

15 (2S)-4-[2-[ethyl[(3-methylphenyl)methyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

(2S)- $\alpha$ -methoxy-4-[2-oxo-2-[(4-phenoxyphenyl)amino]ethoxy]- benzenepropanoic acid;

20 (2S)- $\alpha$ -methoxy-4-[2-[(1-methylhexyl)amino]-2-oxoethoxy]- benzenepropanoic acid;

(2S)-4-[2-[[1,1'-biphenyl]-4-ylmethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

3-[2-[[cis-4-(1,1-dimethylethyl)cyclohexyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

25 (2S)-4-[2-[4-(3-chlorophenyl)-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;

(2S)- $\alpha$ -methoxy-4-[2-[methyl[(1S)-1-phenylethyl]amino]-2-oxoethoxy]- benzenepropanoic acid;

30 (2S)- $\alpha$ -methoxy-4-[2-[4-(4-methylphenyl)-1-piperazinyl]-2-oxoethoxy]- benzenepropanoic acid;

- (2S)- $\alpha$ -methoxy-4-[2-[[3-(methylphenylamino)propyl]amino]-2-oxoethoxy]- benzenepropanoic acid;
- (2S)-4-[2-(cyclobutylamino)-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 5 (2S)- $\alpha$ -methyl-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- $\alpha$ -[4-(trifluoromethoxy)phenoxy]- benzenepropanoic acid;
- (2S)-4-[2-(heptylamino)-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-[4-(4-fluorophenyl)-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 10 (2S)- $\alpha$ -methoxy-4-[2-[[[(1S)-1-(1-naphthalenyl)ethyl]amino]-2-oxoethoxy]- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[[(1R)-1-phenylethyl](phenylmethyl)amino]ethoxy]- benzenepropanoic acid;
- (2S)-4-[2-[(3,3-diphenylpropyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 15 (2S)-4-[2-[[trans-4-(1,1-dimethylethyl)cyclohexyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)- $\alpha$ -methyl-4-[2-oxo-2-[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- $\alpha$ -phenoxy-, ethyl ester- benzenepropanoic acid;
- 20 (2S)-4-[2-[(2,2,3,3,4,4,4-heptafluorobutyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-(3,4-dihydro-2(1H)-isoquinolinyl)-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-3-[2-[[2-(4-ethylphenyl)ethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 25 (2S)- $\alpha$ -methoxy-4-[2-[(1-naphthalenylmethyl)amino]-2-oxoethoxy]- benzenepropanoic acid;
- (2S)-4-[2-[[4-chlorophenyl]phenylmethyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 30 (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[[2-(2-

- pyridinyl)ethyl]amino]ethoxy]- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-oxo-2-[(1S)-1-phenylethyl]amino]ethoxy]- benzenepropanoic acid;
- 5 (2S)-4-[2-(cyclopentylamino)-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 4-[2-[cyclohexyl[2-(4-ethylphenyl)ethyl]amino]-2-oxoethoxy]- $\alpha$ -ethoxy- benzenepropanoic acid;
- 10 (2S)-4-[2-[(1,3-benzodioxol-5-ylmethyl)amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- D-Phenylalanine, N-[[4-[(2S)-2-carboxy-2-methoxyethyl]phenoxy]acetyl]-,  $\alpha$ -methyl ester;
- (2S)-4-[2-[4-[(4-fluorophenyl)methyl]-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 15  $\alpha$ -methoxy-3-[2-oxo-2-[(4-phenoxyphenyl)amino]ethoxy]- benzenepropanoic acid;
- (2S)- $\alpha$ -methoxy-4-[2-[(1-methylbutyl)amino]-2-oxoethoxy]- benzenepropanoic acid;
- 20 (2S)- $\alpha$ -methoxy-4-[2-[methyl(1-naphthalenylmethyl)amino]-2-oxoethoxy]- benzenepropanoic acid;
- (2S)-3-[2-[[trans-4-(1,1-dimethylethyl)cyclohexyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-[4-[(4-chlorophenyl)methyl]-1-piperazinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 25 (2S)-4-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- (2S)-4-[2-[ethyl[(2-fluorophenyl)methyl]amino]-2-oxoethoxy]- $\alpha$ -methoxy- benzenepropanoic acid;
- 30 (2S)- $\alpha$ -methoxy-4-[2-[2-(4-

- methoxyphenoxy)ethyl]amino]-2-oxoethoxy]- benzenepropanoic acid;
- (2S)-4-[2-[(1,3-dimethylbutyl)amino]-2-oxoethoxy]-  
α-methoxy- benzenepropanoic acid;
- 5 (2S)-α-(4-fluorophenoxy)-α-methyl-4-[2-oxo-2-  
[[2-(4-phenoxyphenyl)ethyl]amino]ethoxy]- benzenepropanoic acid;
- (2S)-4-[2-[(3,3-dimethylbutyl)amino]-2-oxoethoxy]-  
α-methoxy- benzenepropanoic acid;
- (2S)-4-[2-[4-(4-chlorophenyl)-3-methyl-1-piperazinyl]-2-  
oxoethoxy]-α-methoxy- benzenepropanoic acid;
- 10 (2S)-α-methoxy-4-[2-oxo-2-[(1R)-1-  
phenylethyl]amino]ethoxy]- benzenepropanoic acid;
- (2S)-4-[2-[4-(4-acetylphenyl)-1-piperazinyl]-2-  
oxoethoxy]-α-methoxy- benzenepropanoic acid;
- (2S)-4-[2-[(3-ethoxy-3-oxopropyl)(phenylmethyl)amino]-2-  
15 oxoethoxy]-α-methoxy- benzenepropanoic acid;
- (2S)-4-[2-[[cis-4-(1,1-dimethylethyl)cyclohexyl]amino]-2-  
oxoethoxy]-α-methoxy- benzenepropanoic acid;
- (2S)-α-ethyl-4-[2-oxo-2-[[2-(4-  
phenoxyphenyl)ethyl]amino]ethoxy]-α-phenoxy- benzenepropanoic acid;
- 20 (2S)-4-[2-(hexylamino)-2-oxoethoxy]-α-methoxy- benzenepropanoic acid;
- (2S)-α-methoxy-4-[2-oxo-2-[(2-  
phenylethyl)(phenylmethyl)amino]ethoxy]- benzenepropanoic acid;
- (2S)-4-[2-[ethyl[2-(4-methoxyphenyl)-1-  
methylethyl]amino]-2-oxoethoxy]-α-methoxy- benzenepropanoic acid;
- 25 [[4-[2-oxo-2-[[phenyl[2-(1-piperidiny)phenyl]methyl]amino]ethyl]phenyl]methyl]-,  
diethyl ester-propanedioic acid;
- 4-[2-(heptylamino)-2-oxoethyl]-α,α-  
dimethyl-, ethyl ester - benzenepropanoic acid;
- 2-[[4-(2-amino-2-oxoethoxy)phenyl]methylene]-3-oxo-, methyl  
30 ester -butanoic acid;

4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]- $\alpha$ -phenyl-,ethyl ester- benzenepropanoic acid;

4-[2-(heptylamino)-2-oxoethyl]- $\alpha,\alpha$ -  
dimethyl-, ethyl ester - benzenepropanoic acid;

4-[2-[[2-[[[(1,1-dimethylethoxy)carbonyl]methylamino]-4-hydroxyphenyl]amino]-2-oxoethoxy]- $\alpha$ -(methylthio)-, ethyl ester-benzenepropanoic acid;

[[4-[2-oxo-2-[[phenyl[2-(1-piperidiny)phenyl]methyl]aminoethyl]phenyl]methyl]-propanedioic acid;

N-[3-[4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]phenyl]-1-oxo-2-phenylpropyl]-, methyl ester - glycine;

4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]- $\alpha$ -phenyl-benzenepropanoic acid;

N-[3-[4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]phenyl]-1-oxo-2-phenylpropyl]-glycine;

or

4-[3-[methyl(2-phenylethyl)amino]-3-oxopropyl]- $\alpha$ -phenyl-benzenepropanoic acid.

Particularly  $R^5$  and  $R^6$  are independently selected substituents, comprising C, H, N, O, S or halogen atoms, which give compounds of the General Formula I a molecular weight < 650.

Alternatively,  $R^5$  and  $R^6$  are independently selected substituents, comprising C, N, O, S, Se, P or halogen atoms. 10. According to one aspect of the invention, when either of  $R^5$  and  $R^6$  is hydrogen, the other is not an alkyl.

Particularly  $R^5$  and  $R^6$  independently represent hydrogen,  $C_{1-13}$ alkyl,  $C_{2-10}$ alkenyl or

$C_{2-10}$ alkynyl each of which is optionally substituted by one or more of the following which may be the same or different:  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkenyl, aryl, heterocyclyl, heteroaryl,  $C_{1-8}$ alkoxy (optionally substituted by one or more fluoro),  $C_{3-8}$ cycloalkoxy,  $C_{3-8}$ cycloalkenyloxy, aryloxy, heterocyclyloxy, heteroaryloxy,  $C_{3-8}$ cycloalkyl  $C_{1-8}$ alkoxy, aryl  $C_{1-8}$ alkoxy, heterocyclyl  $C_{1-8}$ alkoxy or heteroaryl  $C_{1-8}$ alkoxy, fluorine or hydroxy and wherein each of these substituents may optionally be substituted on carbon with one or more substituents which may be the same or different and selected from  $C_{1-8}$ alkyl,  $C_{3-8}$ cycloalkyl (optionally substituted by  $C_{1-8}$ alkyl,  $C_{1-8}$ alkoxy (optionally substituted by one

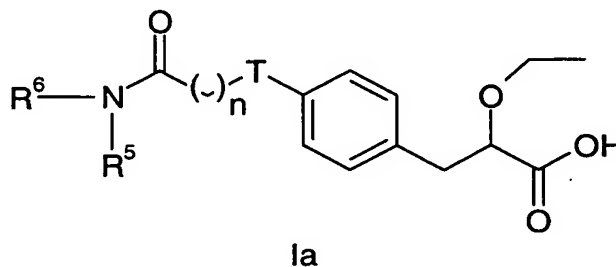


or more fluoro), halogen, hydroxy, nitro or cyano), aryl (optionally substituted by C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkoxy (optionally substituted by one or more fluoro), halogen, hydroxy, nitro or cyano), heterocyclyl (optionally substituted by C<sub>1-6</sub>alkyl on any nitrogen), heteroaryl (optionally substituted by C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkoxy (optionally substituted by one or more fluoro), halogen, hydroxy, nitro or cyano), C<sub>1-8</sub>alkoxy (optionally substituted by one or more fluoro), C<sub>3-8</sub>cycloalkoxy, C<sub>3-8</sub> cycloalkyl C<sub>1-8</sub>alkoxy, aryloxy (optionally substituted by C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkoxy (optionally substituted by one or more fluoro), halogen, hydroxy, nitro or cyano), aryl C<sub>1-8</sub>alkoxy (wherein the aryl part is optionally substituted by C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkoxy (optionally substituted by one or more fluoro), halogen, hydroxy, nitro or cyano), halogen, amino, nitro, hydroxy, methylsulfonyl, methylsulfonyloxy, cyano or methylenedioxy,

or R<sup>5</sup> and R<sup>6</sup> independently represent C<sub>3-8</sub> cycloalkyl; C<sub>3-8</sub> cycloalkenyl; aryl; heterocyclyl; or heteroaryl; wherein each of these groups is optionally substituted by one or more of the following: C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkoxy (optionally substituted by one or more fluoro), halogen, hydroxy, nitro or cyano), aryl (optionally substituted by C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkoxy (optionally substituted by one or more fluoro), halogen, hydroxy, nitro or cyano; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a single or a fused heterocyclic system.

Particularly A is CH<sub>2</sub>CH(OR<sup>t</sup>)COOR<sup>m</sup> wherein R<sup>t</sup> represents C<sub>1-4</sub>alkyl and wherein R<sup>m</sup> represents H or C<sub>1-4</sub>alkyl.

A preferred group of compounds is represented by formula Ia



as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof

wherein;

5

T represents O or a single bond;

n = 1 or 2;

R<sup>5</sup> and R<sup>6</sup> are independently selected C<sub>1-10</sub>alkyl (optionally substituted by one or more C<sub>1-4</sub>alkoxy); C<sub>5-7</sub>cycloalkylC<sub>1-4</sub>alkyl (optionally substituted cyano); benzyl or phenethyl  
10 (each of which is optionally substituted by one or more of the following: halo; C<sub>1-4</sub>alkyl; C<sub>1-4</sub>alkoxy; trifluoromethyl; trifluoromethoxy; methylenedioxy; phenyl; benzyloxy; methanesulfonyloxy); indolylmethyl; or thienylmethyl.

In preferred groups of compounds of formula I and formula Ia, R<sup>5</sup> represents C<sub>1-10</sub>alkyl  
15 (optionally substituted by one or more C<sub>1-4</sub>alkoxy) and R<sup>6</sup> represents benzyl optionally substituted one or more of the following: halo; C<sub>1-4</sub>alkyl; C<sub>1-4</sub>alkoxy; trifluoromethyl; trifluoromethoxy; methylenedioxy; phenyl; benzyloxy or methanesulfonyloxy.

Alternatively n represents 2, 3 or 4.

20

In other preferred groups of compounds of formula I and Ia R<sup>5</sup> and R<sup>6</sup> independently represent benzyl optionally substituted one or more of the following: halo; C<sub>1-4</sub>alkyl; C<sub>1-4</sub>alkoxy; trifluoromethyl; trifluoromethoxy; methylenedioxy; phenyl; benzyloxy or  
methanesulfonyloxy.

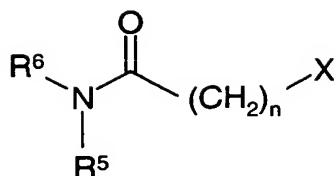
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R<sup>3</sup> and R<sup>4</sup> may be the same or different and each represents alkyl, aryl or alkylaryl.  
Alternatively R<sup>3</sup> and R<sup>4</sup> are hydrogen.

In one aspect of the invention R<sup>2</sup> is hydrogen or fluorine.

30

A compound of formula VI:



VI

wherein R<sup>5</sup>, R<sup>6</sup> and n is as defined in any of the preceding claims and X is a leaving group, such as a halide, OSO<sub>2</sub>CH<sub>3</sub>, OTosyl, ONosyl, OSO<sub>2</sub>CF<sub>3</sub>, OC(O)OR, OP(O)(OR)<sub>2</sub> or OSO<sub>2</sub>OR, particularly chloro or bromo. Formula VI is useful as an intermediate in the process of manufacturing formula I.

The following definitions shall apply throughout the specification and the appended claims with regard to the group A.

Unless otherwise stated or indicated, the term "alkyl" denotes a straight or branched, substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms or a cyclic alkyl having from 3 to 6 carbon atoms. The term "lower alkyl" denotes a straight or branched, substituted or unsubstituted alkyl group having from 1 to 3 carbon atoms or a cyclic alkyl having 3 carbon atoms. Examples of said alkyl and lower alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl as well as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

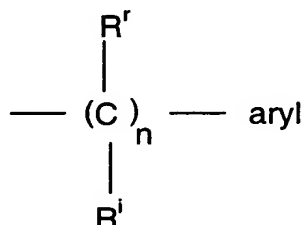
Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

Unless otherwise stated or indicated, the term "aryl" denotes a substituted or unsubstituted phenyl, furyl, thienyl or pyridyl group, or a fused ring system of any of these groups, such as naphthyl.

Unless otherwise stated or indicated, the term "substituted" denotes an alkyl or an aryl group as defined above which is substituted by one or more alkyl, alkoxy, halogen, amino, thiol, nitro, hydroxy, acyl, aryl or cyano groups.

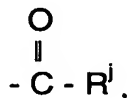
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Unless otherwise stated or indicated, the term "alkylaryl" denotes a



10 wherein n is an integer 1 to 6 and  $\text{R}^{\text{r}}$  and  $\text{R}^{\text{i}}$  are the same or different and each represents hydrogen or an alkyl or aryl group as defined above.

Unless otherwise stated or indicated, the term "acyl" denotes a group



15

wherein  $\text{R}^{\text{j}}$  is hydrogen, alkyl, alkoxy, aryl and alkylaryl as defined above.

20 Unless otherwise stated or indicated, the terms "alkenyl" and "alkynyl" denote a straight or branched, substituted or unsubstituted unsaturated hydrocarbon group having one or more double or triple bonds and having a maximum of 6 carbon atoms, preferably 3 carbon atoms.

25 Unless otherwise stated or indicated the term "protective group" ( $\text{R}^{\text{p}}$ ) denotes a protecting group as described in the standard text "Protecting groups in Organic Synthesis", 2nd

Edition (1991) by Greene and Wuts. The protective group may also be a polymer resin such as Wang resin or 2-chlorotrityl chloride resin.

For the groups other than A the following definitions apply.

5 "Cycloalkyl" means a non-aromatic monocyclic or multicyclic ring system of from 3 carbon atoms up to 10 carbon atoms.

"Aryl" means an aromatic monocyclic or multicyclic ring system of up to 14 carbon atoms.

10 "Heterocyclyl" means a non-aromatic monocyclic or multicyclic ring system of up to 14 carbon atoms, containing at least one heteroatom .

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of up to 14 carbon atoms, containing at least one heteroatom.

15

The term "prodrug " as used in this specification includes derivatives of the carboxylic acid group which are converted in a mammal, particularly a human, into the carboxylic acid group or a salt or conjugate thereof. It should be understood that, whilst not being bound by theory, it is believed that most of the activity associated with the prodrugs arises from the activity of the compound of formula I into which the prodrugs are converted. Prodrugs can be prepared by routine methodology well within the capabilities of someone skilled in the art. Various prodrugs of carboxy are known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in  
25 Enzymology. 42: 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p.113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8:1-38 (1992);
- 30 d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77:285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32:692 (1984).

The above documents a to e are herein incorporated by reference.

*In vivo* cleavable esters are just one type of prodrug of the parent molecule. An *in vivo* hydrolysable (or cleavable) ester of a compound of the formula (I) that contains a carboxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid. Suitable pharmaceutically acceptable esters for carboxy include C<sub>1-6</sub>alkoxymethyl esters, for example, methoxymethyl; C<sub>1-6</sub>alkanoyloxymethyl esters, for example, pivaloyloxymethyl; phthalidyl esters; C<sub>3-8</sub>cycloalkoxycarbonyloxyC<sub>1-6</sub>alkyl esters, for example, 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example, 5-methyl-1,3-dioxolen-2-onylmethyl; and C<sub>1-6</sub>alkoxycarbonyloxyethyl esters, for example, 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

Specific compounds of the invention are:

- (2*S*)-3-(4-{2-[(2,4-Difluorobenzyl)(octyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(2,4-Difluorobenzyl)(nonyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(2,4-Difluorobenzyl)(4-ethylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[Benzyl(methyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-Ethoxy-3-[4-(2-{heptyl[(1-methylindol-2-yl)methyl]amino}-2-oxoethoxy)phenyl]propanoic acid
- (2*S*)-3-(4-{2-[(2,3-Dimethoxybenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[Butyl(2,3-dimethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(4-Chlorobenzyl)(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(Cyclohexylmethyl)(2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-Ethoxy-3-(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- (2*S*)-3-(4-{2-[[4-(benzyloxy)benzyl](butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

- (2*S*)-3-(4-{2-[bis(4-Chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(4-*tert*-Butylbenzyl)(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-[4-(2-{(4-Chlorobenzyl)[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid
- 5 (2*S*)-3-[4-(2-{bis[4-(Trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[Benzyl(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid and
- (2*S*)-3-(4-{2-[(4-*tert*-Butylbenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 10 (2*S*)-3-(4-{2-[benzyl(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-ethoxy-3-(4-{2-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- (2*S*)-3-(4-{2-[butyl(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 15 (2*S*)-3-(4-{2-[(2-chlorobenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-ethoxy-3-(4-{2-[heptyl(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- 20 (2*S*)-3-(4-{2-[[4-(cyanocyclohexyl)methyl](4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-ethoxy-3-(4-{2-[(4-isopropylbenzyl)(2-methoxybenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- (2*S*)-3-(4-{2-[(2-chlorobenzyl)(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 25 (2*S*)-3-(4-{2-[(4-chlorobenzyl)(2,3-dimethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(1,3-benzodioxol-5-ylmethyl)(4-ethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 30 (2*S*)-3-(4-{2-[(1,3-benzodioxol-5-ylmethyl)(3-bromobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

- (2*S*)-3-[4-(2-((1,3-benzodioxol-5-ylmethyl)[3-(trifluoromethyl)benzyl]amino)-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid
- (2*S*)-3-(4-(2-((3,5-dimethoxybenzyl)(4-ethoxybenzyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- 5 (2*S*)-3-(4-(2-((3-chloro-4-fluorobenzyl)(4-ethoxybenzyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-ethoxy-3-(4-(2-((4-ethoxybenzyl)(2-thienylmethyl)amino)-2-oxoethoxy)phenyl)propanoic acid
- (2*S*)-3-(4-(2-((benzyl(isopropyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- 10 (2*S*)-3-(4-(2-((dibenzylamino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-(2-((bis(2-methoxyethyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-ethoxy-3-[4-(2-((heptyl[4-(trifluoromethyl)benzyl]amino)-2-oxoethoxy)phenyl)]propanoic acid
- (2*S*)-2-ethoxy-3-[4-(2-((heptyl[4-(trifluoromethoxy)benzyl]amino)-2-oxoethoxy)phenyl)]propanoic acid
- 15 (2*S*)-2-ethoxy-3-(4-(2-((4-ethylbenzyl)(heptyl)amino)-2-oxoethoxy)phenyl)propanoic acid
- (2*S*)-3-(4-(2-((4-*tert*-butylbenzyl)(heptyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-ethoxy-3-(4-(2-((heptyl(4-isobutylbenzyl)amino)-2-oxoethoxy)phenyl)propanoic acid
- 20 acid
- (2*S*)-3-(4-(2-((benzyl(heptyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-ethoxy-3-(4-(2-((4-fluorobenzyl)(heptyl)amino)-2-oxoethoxy)phenyl)propanoic acid
- acid
- (2*S*)-3-(4-(2-((4-chlorobenzyl)(heptyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- 25 acid
- (2*S*)-3-(4-(2-((4-bromobenzyl)(heptyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- acid
- (2*S*)-3-(4-(2-((butyl(4-ethylbenzyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-(2-((butyl(4-*tert*-butylbenzyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- 30 acid
- (2*S*)-3-(4-(2-((butyl(4-isobutylbenzyl)amino)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid
- acid



(2S)-3-(4-{2-[benzyl(butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2S)-3-(4-{2-[butyl(4-fluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2S)-3-(4-{2-[(4-bromobenzyl)(butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

5 (2S)-3-(4-{2-[butyl(2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2S)-3-[4-(2-{(4-chlorobenzyl)[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

10 (2S)-3-(4-{2-[(4-chlorobenzyl)(4-ethylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2S)-3-(4-{2-[(4-chlorobenzyl)(4-isobutylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2S)-3-(4-{2-[benzyl(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

15 (2S)-3-(4-{2-[(4-chlorobenzyl)(4-fluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2S)-3-(4-{2-[(4-bromobenzyl)(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2S)-3-(4-{2-[(4-chlorobenzyl)(2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

20 (2S)-2-ethoxy-3-[4-(2-{(4-methylbenzyl)[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]propanoic acid

(2S)-2-ethoxy-3-[4-(2-{(4-methylbenzyl)[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]propanoic acid

25 (2S)-2-ethoxy-3-(4-{2-[(4-ethylbenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2S)-3-(4-{2-[(4-*tert*-butylbenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2S)-2-ethoxy-3-(4-{2-[(4-isobutylbenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid

30 (2S)-3-(4-{2-[benzyl(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2*S*)-2-ethoxy-3-(4-{2-[(4-fluorobenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2*S*)-3-(4-{2-[(4-chlorobenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

5 (2*S*)-3-(4-{2-[(4-bromobenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2*S*)-3-(4-{2-[(2,4-difluorobenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

and pharmaceutically acceptable salts thereof.

10 In the present specification the expression "pharmaceutically acceptable salts" is intended to define but is not limited to salts with bases.

It will also be understood that certain compounds of the present invention may exist in solvated as well as unsolvated forms. It is to be understood that the present invention  
15 encompasses all such solvated forms. Certain compounds of the present invention may exist as tautomers. It is to be understood that the present invention encompasses all such tautomers.

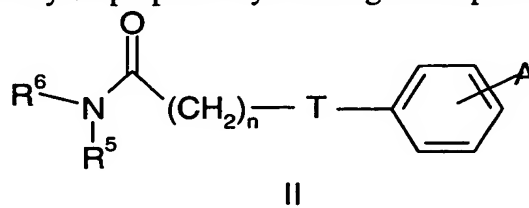
### Methods of preparation

20

The compounds of the invention may be prepared as outlined below. However, the invention is not limited to these methods. The compounds may also be prepared as described for structurally related compounds in the prior art. The reactions can be carried out according to standard procedures or as described in the experimental section.

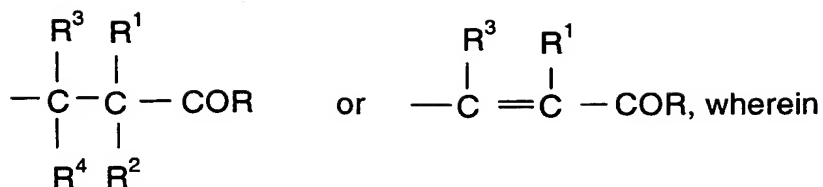
25

Compounds of formula I may be prepared by reacting a compound of formula II



wherein

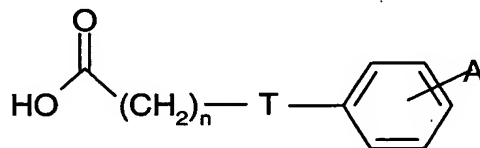
A is situated in the ortho, meta or para position and represents



in which  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are as previously defined and  $\text{R}$  represents  $-\text{OR}^{\text{P}}$ , wherein  $\text{R}^{\text{P}}$  is a protecting group for a carboxylic hydroxy group as described in the standard text  
 5 "Protective Groups in Organic Synthesis", 2<sup>nd</sup> Edition (1991) by Greene and Wuts, with a de-protecting agent. The protecting group may also be a resin, such as Wang resin or 2-chlorotriyl chloride resin. Protecting groups may be removed in accordance to techniques that are well known to those skilled in the art. One such protecting group is where  $-\text{OR}^{\text{P}}$  represents a  $\text{C}_{1-6}$ alkoxy group or an arylalkoxy group eg benzyloxy, such that  $\text{COR}^{\text{P}}$   
 10 represents an ester. Such esters can be reacted with a de-protecting agent e.g. a hydrolysing agent, for example lithium hydroxide in a mixture of THF and water, at a temperature in the range of 0-100°C to give compounds of formula I.

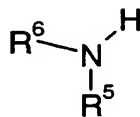
Compounds of formula II may be prepared by reacting a compound of formula III

15



III

in which A, T and n are as previously defined with a compound of formula IV

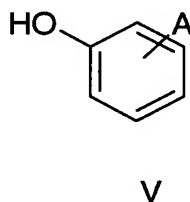


IV

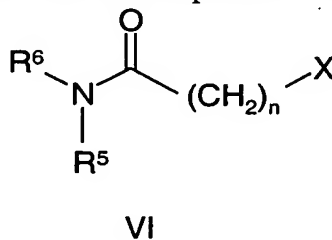
in which  $R^5$  and  $R^6$  are as previously defined in an inert solvent, for example dichloromethane, in the presence of a coupling agent, for example a carbodiimide, eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or oxalyl chloride, optionally in the presence of a base particularly diisopropylethyl amine, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylaminopyridine, at a temperature in the range of  $-25^\circ\text{C}$  to  $150^\circ\text{C}$ .

Compounds of formulae III and IV may be prepared by methods described in the Examples or by analogous methods known to those skilled in the art.

Compounds of formula II may be prepared by reacting a compound of formula V



in which A is as previously defined with a compound of formula VI



in which  $R^5$  and  $R^6$  are as previously defined and X represents a leaving group, for example a halide,  $\text{OSO}_2\text{CH}_3$ , OTosyl, ONosyl,  $\text{OSO}_2\text{CF}_3$ ,  $\text{OC}(\text{O})\text{OR}$ ,  $\text{OP}(\text{O})(\text{OR})_2$  or  $\text{OSO}_2\text{OR}$ , particularly chloro or bromo, in an inert solvent, for example acetonitrile, methyl isobutylketone, *N*-methylpyrrolidone, toluene, toluene/water, ethanol or isopropylacetate in the presence of a base, for example potassium carbonate, sodium hydroxide or triethylamine, at a temperature in the range of  $-25^\circ\text{C}$  to  $150^\circ\text{C}$ . Optionally a catalyst may be used for example iodide or a quaternary ammonium salt, particularly sodium iodide or tetra-*n*-butylammonium -iodide, -bromide, -acetate or -hydrogensulphate.

Compounds of formulae V and VI may be prepared by methods described in the Examples or by analogous methods known to those skilled in the art.

5

Formulae VI can be:

2-chloro-*N*-(2,4-difluorobenzyl)-*N*-octylacetamide

2-chloro-*N*-(2,4-difluorobenzyl)-*N*-nonylacetamide

10

2-chloro-*N*-(2,4-difluorobenzyl)-*N*-(4-ethylbenzyl)acetamide

2-chloro-*N*-(2,4-difluorobenzyl)-*N*-methylacetamide

15

2-chloro-*N*-heptyl-*N*-[(1-methyl-1*H*-indol-2-yl)methyl]acetamide

2-chloro-*N*-(2,3-dimethoxybenzyl)-*N*-heptylacetamide

*N*-butyl-2-chloro-*N*-(2,3-dimethoxybenzyl)acetamide

20

2-chloro-*N*-(4-chlorobenzyl)-*N*-(4-isopropylbenzyl)acetamide

2-chloro-*N*-(cyclohexylmethyl)-*N*-(2,4-difluorobenzyl)acetamide

25

2-chloro-*N*-ethyl-*N*-(2-fluorobenzyl)acetamide

*N*-[4-(benzyloxy)benzyl]-*N*-butyl-2-chloroacetamide

2-chloro-*N*-hexyl-*N*-(2-phenylethyl)acetamide

30

2-chloro-*N,N*-bis(4-chlorobenzyl)acetamide

*N*-(4-*tert*-butylbenzyl)-2-chloro-*N*-(4-chlorobenzyl)acetamide

5 2-chloro-*N*-(4-chlorobenzyl)-*N*-[4-(trifluoromethyl)benzyl]acetamide

2-chloro-*N,N*-bis[4-(trifluoromethyl)benzyl]acetamide

*N*-benzyl-2-chloro-*N*-ethylacetamide

10

*N*-(4-*tert*-butylbenzyl)-2-chloro-*N*-ethylacetamide

2-chloro-*N*-ethyl-*N*-[4-(trifluoromethyl)benzyl]acetamide

15

2-chloro-*N*-(4-cyclohexylbutyl)-*N*-(2,4-difluorobenzyl)acetamide

*N*-(2-biphenyl-4-ylethyl)-2-chloro-*N*-(2,4-difluorobenzyl)acetamide

2-chloro-*N*-(4-chlorobenzyl)-*N*-(2-methoxybenzyl)acetamide

20

4-{[butyl(chloroacetyl)amino]methyl}phenyl methanesulfonate

25

Compounds of formulae II, III, IV, V and VI are useful intermediates in the preparation of compounds of formula I. Compounds of formula II, III, V and VI are herein claimed as a further aspect of the present invention. The *S*-enantiomers of compounds of formula II, III and V are preferred. The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

30

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process

steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

5

The expression "inert solvent" refers to a solvent that does not react with the starting materials, reagents, intermediates or products in a manner that adversely affects the yield of the desired product.

#### 10 Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutical  
15 acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in therapeutical treatment of  
20 humans are about 0.0001-100 mg/kg body weight, preferably 0.001-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in  
25 the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically

acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

#### Pharmacological properties

5 The present compounds of formula (I) are useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type  
10 2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of  
15 small, dense, low density lipoproteins (LDL) particles, phenotype B.

The compounds of the present invention are expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and postprandial dyslipidemia with or without other manifestations of the metabolic syndrome.

20

Treatment with the present compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart  
25 failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of their insulin sensitizing effect the compounds of formula I are also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic hyperglycaemia in diabetes mellitus such as the  
30 micro-angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed. Furthermore the compounds may be useful in treatment of various conditions outside the cardiovascular system whether or not



associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease and multiple sclerosis.

5 The compounds of the present invention are expected to be useful in controlling glucose levels in patients suffering from type 2 diabetes.

The present invention provides a method of treating or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the  
10 administration of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of formula I to a  
15 mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of formula I as a medicament.

20 In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

#### Combination Therapy

25 The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. The compounds of the invention may be combined with another therapeutic agent  
30 that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may

also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include  
5 biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is  
10 repaglinide or nateglinide.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with another PPAR modulating agent. PPAR modulating agents include but are  
15 not limited to a PPAR alpha and/or gamma and /or delta agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO  
20 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to BMS 298585, clofibrate, fenofibrate, bezafibrate, gemfibrozil and ciprofibrate; GW 9578, pioglitazone,  
25 rosiglitazone, rivoglitazone, balaglitazone, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxy-phenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

30 In addition the combination of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide,

glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolclamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. Therefore the present invention includes administration of a compound of the present invention in  
5 conjunction with one, two or more existing therapies described in this paragraph. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA.

Alternatively smaller doses may be used as a result of the benefits derived from the  
10 combination. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, bervastatin,  
15 cerivastatin, dalvastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly  
20 preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[N-methyl-N-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid  
] or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The  
25 compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl-(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now known under its generic name rosuvastatin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

5 The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

The present invention also includes a compound of the present invention in combination  
10 with an inhibitor of the ileal bile acid transport system (IBAT inhibitor).

Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818,  
15 WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595 and  
20 EP624596 and the contents of these patent applications are incorporated herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepinines, and the compounds described in the claims, particularly claim 1, of WO  
25 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

30 One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl  $\beta$ -D-glucopyranosiduronic acid (EP 864 582). Other suitable IBAT inhibitors include one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(5-carboxypentyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)- $\alpha$ -(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{ $\alpha$ -[*N'*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{ $\alpha$ -[*N'*-(ethoxy)(methyl)phosphoryl-methyl]carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)- $\alpha$ -(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)- $\alpha$ -(*N'*-{2-[(methyl)(ethyl)phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)- $\alpha$ -(*N'*-{2-[(methyl)(hydroxy)phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)- $\alpha$ -[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R/S)- $\alpha$ -{*N*-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;

a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;

a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;

a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and niceritrol;

a phytosterol compound for example stanols; probucol;

an omega-3 fatty acid for example Omacor<sup>TM</sup>;



an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha

adrenergic blocker, a beta adrenergic blocker for example metoprolol, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-

blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with a compound of formula I include but are not limited to, the following compounds:

alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide,trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and

enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of  
5 such salts or a prodrugs thereof for use in combination with a compound of formula I include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

10 Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt,  
15 solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

20 Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an  
25 effective amount of one the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable  
30 salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate

of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a  
5 compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

- 10 According to a further aspect of the present invention there is provided a kit comprising:
- a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
  - b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage  
15 form; and
  - c) container means for containing said first and second dosage forms.

- According to a further aspect of the present invention there is provided a kit comprising:
- a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such  
20 a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
  - b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
  - 25 c) container means for containing said first and second dosage forms.

- According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or  
30 a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or  
5 a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination  
10 treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable  
15 salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

### Examples

20

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at  $^1\text{H}$  frequencies of 300, 400, 500 and 600 MHz, respectively, and at  $^{13}\text{C}$  frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale ( $\delta$ ).

25

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

### Abbreviations

DMSO	dimethyl sulfoxide
30 THF	tetrahydrofuran
Pd/C	palladium on charcoal
DMAP	dimethylaminopyridine

t	triplet
s	singlet
d	doublet
q	quartet
5 m	multiplet
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublet

#### 10 Example 1

(2S)-3-(4-{2-[(2,4-Difluorobenzyl)(octyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

##### (i) N-(2,4-Difluorobenzyl)octanamide

To a solution of 2,4-difluorobenzylamine (0.43 g, 3.0 mmol) in methylene chloride (30 mL) were added octanoic acid (0.43 g, 3.0 mmol) and DMAP (0.37 g, 3.0 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.60 g, 3.1 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (100 mL) and the organic phase was washed with 5% HCl (3 x 75 mL), aqueous NaHCO<sub>3</sub> (75 mL), and brine (75 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* afforded 0.78 g (96%) of an oil, which solidified upon standing.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 0.81–0.90 (m, 3H), 1.18–1.33 (m, 8H), 1.54–1.66 (m, 2H), 2.12–2.21 (m, 2H), 4.42(d, 2H), 5.82 (bs, 1H), 6.73–6.87 (m, 2H), 7.32 (m, 1H).

##### 25 (ii) N-(2,4-Difluorobenzyl)-N-octylamine hydrochloride

N-(2,4-Difluorobenzyl)octanamide (0.64 g, 2.4 mmol) was dissolved in freshly distilled THF (20 mL) and cooled on an ice bath under an argon atmosphere. Borane (3.0 mL of a 2 M solution of the dimethylsulfide complex in diethyl ether) was added and the ice bath was removed after 15 minutes. The reaction mixture was refluxed for twenty hours and was then allowed to cool to room temperature. The reaction was quenched by careful addition of 10% HCl (1.2 mL) and the mixture was stirred overnight and then concentrated *in*

*vacuo*. Addition of ice cold THF (15 mL) afforded a white precipitate, which was filtered off and dried *in vacuo* to give 0.40 g (58%) of a white salt.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 0.85–0.93 (m, 3H), 1.20–1.45 (m, 10H), 1.65–1.89 (m, 2H), 3.01–3.09 (m, 2H), 4.25 (s, 2H), 7.04–7.16 (m, 2H), 7.63 (m, 1H).

(iii) Ethyl (2*S*)-3-(4-{2-[(2,4-difluorobenzyl)(octyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.120 g, 0.40 mmol) in methylene chloride (5.0 mL) were added *N*-(2,4-difluorobenzyl)-*N*-octylamine hydrochloride (0.165 g, 0.57 mmol), DMAP (0.054 g, 0.45 mmol) and *N,N*-diisopropylethylamine (0.078 mL, 0.45 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.085 g, 0.45 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (50 mL) and the organic phase was washed with 5% HCl (3 x 25 mL), aqueous NaHCO<sub>3</sub> (25 mL), and brine (25 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute<sup>®</sup> SPE Column, 5 g Si/25 mL) with methanol (0–1% gradient) in methylene chloride as the eluent afforded 0.082 g (38%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.80–0.90 (m, 3H), 1.14 (t, 3H), 1.17–1.30 (m, 13H), 1.42–1.64 (m, 2H), 2.86–3.00 (m, 2H), 3.20–3.40 (m, 3H), 3.59 (m, 1H), 3.95 (m, 1H), 4.15 (q, 2H), 4.59 (s, 2H), 4.69 and 4.70 (2s, 2H, rotamers), 6.71–6.88 (m, 4H), 7.07–7.18 and 7.20–7.31 (2m, 3H, rotamers).

(iv) (2*S*)-3-(4-{2-[(2,4-Difluorobenzyl)(octyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-(4-{2-[(2,4-difluorobenzyl)(octyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.038 g, 0.071 mmol) in THF (3 mL) was added aqueous 0.10 M LiOH (2 mL) and the reaction mixture was stirred at room temperature overnight. After acidification with 5% HCl, the mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic phase was washed with brine (25 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.035 g (98%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.83–0.93 (m, 3H), 1.17 (t, 3H), 1.20–1.35 (m, 10H), 1.42–1.68 (m, 2H), 2.88–3.10 (m, 2H), 3.24–3.35 (m, 2H), 3.41 (m, 1H), 3.62 (m, 1H), 4.03 (m, 1H), 4.62 (s, 2H), 4.72 and 4.73 (2s, 2H, rotamers), 6.70–6.90 (m, 4H), 7.09–7.21 and 7.24–7.34 (2m, 3H, rotamers).

5

### Example 2

(2S)-3-(4-{2-[(2,4-Difluorobenzyl)(nonyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

#### (i) *N*-(2,4-Difluorobenzyl)nonanamide

10 To a solution of 2,4-difluorobenzylamine (0.47 g, 3.3 mmol) in methylene chloride (30 mL) were added nonanoic acid (0.52 g, 3.3 mmol) and DMAP (0.40 g, 3.3 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.67 g, 3.5 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (100 mL) and the organic phase was washed with 5% HCl  
15 (3 x 75 mL), aqueous NaHCO<sub>3</sub> (75 mL), and brine (75 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* afforded 0.87 g (93%) of an oil, which solidified upon standing.

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 0.80–0.86 (m, 3H), 1.16–1.28 (m, 10 H), 1.53–1.62 (m, 2H), 2.11–2.17 (m, 2H), 4.37 (d, 2H), 6.12 (bs, 1H), 6.70–6.81 (m, 2H), 7.27 (m, 1H).

20

#### (ii) *N*-(2,4-Difluorobenzyl)-*N*-nonylamine hydrochloride

*N*-(2,4-Difluorobenzyl)nonanamide (0.75 g, 2.6 mmol) was dried once by azeotropic distillation with toluene, dissolved in freshly distilled THF (23 mL), and cooled on an ice bath under an argon atmosphere. Borane (3.3 mL of a 2 M solution of the dimethylsulfide  
25 complex in diethyl ether) was added and the ice bath was removed after 15 minutes. The reaction mixture was refluxed for five hours and was then allowed to cool to room temperature. The reaction was quenched by careful addition of 10% HCl (1.3 mL) and the mixture was stirred for three hours and then concentrated *in vacuo*. Addition of ice cold THF (15 mL) afforded a white precipitate, which was filtered off and dried *in vacuo* to  
30 give 0.69 g (85%) of a white salt.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 0.85–0.94 (m, 3H), 1.20–1.45 (m, 12H), 1.65–1.80 (m, 2H), 3.00–3.10 (m, 2H), 4.26 (s, 2H), 7.04–7.16 (m, 2H), 7.64 (m, 1H).

(iii) Ethyl (2S)-3-(4-{2-[(2,4-difluorobenzyl)(nonyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.120 g, 0.40 mmol) in methylene chloride (5.0 mL) were added (*N*-(2,4-difluorobenzyl)-*N*-nonylamine hydrochloride (0.173 g, 0.57 mmol), DMAP (0.058 g, 0.45 mmol), and *N,N*-diisopropylethylamine (0.078 mL, 0.45 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.085 g, 0.45 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (50 mL) and the organic phase was washed with 5% HCl (3 x 25 mL), aqueous NaHCO<sub>3</sub> (25 mL), and brine (25 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 5 g Si/25 mL) with methanol (0–1% gradient) in methylene chloride as the eluent afforded 0.117 g (53%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.82–0.90 (m, 3H), 1.14 (t, 3H), 1.17–1.30 (m, 15H), 1.42–1.62 (m, 2H), 2.88–3.00 (m, 2H), 3.23–3.38 (m, 3H), 3.58 (m, 1H), 3.95 (m, 1H), 4.14 (q, 2H), 4.59 (s, 2H), 4.68 and 4.69 (2s, 2H, rotamers), 6.70–6.90 (m, 4H), 7.06–7.18 and 7.20–7.31 (2m, 3H, rotamers).

(iv) (2S)-3-(4-{2-[(2,4-Difluorobenzyl)(nonyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2S)-3-(4-{2-[(2,4-difluorobenzyl)(nonyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.038 g, 0.070 mmol) in THF (3 mL) was added aqueous 0.10 M LiOH (2 mL) and the reaction mixture was stirred at room temperature overnight. After acidification with 5% HCl, the mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic phase was washed with brine (25 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.034 g (94%) of a colourless oil.



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.83–0.93 (m, 3H), 1.17 (t, 3H), 1.20–1.35 (m, 12H), 1.44–1.66 (m, 2H), 2.90–3.10 (m, 2H), 3.25–3.34 (m, 2H), 3.42 (m, 1H), 3.62 (m, 1H), 4.04 (m, 1H), 4.62 (s, 2H), 4.72 and 4.73 (2s, 2H, rotamers), 6.73–6.90 (m, 4H), 7.09–7.21 and 7.24–7.34 (2m, 3H, rotamers).

5

### Example 3

(2S)-3-(4-{2-[2-(2,4-Difluorobenzyl)(4-ethylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

#### (i) N-(2,4-Difluorobenzyl)-4-ethylbenzamide

10 To a solution of 2,4-difluorobenzylamine (3.58 g, 25.0 mmol) in methylene chloride (250 mL) were added 4-ethylbenzoic acid (3.94 g, 26.3 mmol) and DMAP (3.36 g, 27.5 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.27 g, 27.5 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was washed with 5% HCl (3 x 100 mL), saturated aqueous NaHCO<sub>3</sub> (100 mL), and  
15 brine (100 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* afforded 6.49 g (94%) of white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.24 (t, 3H), 2.69 (q, 2H), 4.64 (d, 2H), 6.45 (bs, 1H), 6.77–6.90 (m, 2H), 7.25 (d, 2H), 7.41 (m, 1H), 7.69 (d, 2H).

#### 20 (ii) N-(2,4-Difluorobenzyl)-N-(4-ethylbenzyl)amine

*N*-(2,4-Difluorobenzyl)-4-ethylbenzamide (6.20 g, 22.5 mmol) was dissolved in freshly distilled THF (220 mL) and cooled in an ice bath under an argon atmosphere. Borane (28 mL of a 2 M solution of the dimethylsulfide complex in diethyl ether) was added and the ice bath was removed after 15 minutes. The reaction mixture was refluxed overnight and was then  
25 allowed to cool to room temperature. The reaction was quenched at 0 °C by careful addition of 10% HCl (11 mL) and the mixture was stirred at room temperature for three hours and then concentrated *in vacuo*. The residue was taken up in ethyl acetate (200 mL) and aqueous 2 M K<sub>2</sub>CO<sub>3</sub> (200 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 200 mL) and the combined organic phase was washed with brine (100 mL), dried  
30 over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 5.56 g (94%) of a yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.24 (t, 3H), 2.65 (q, 2H), 3.77 (s, 2H), 3.82 (s, 2H), 6.75–6.90 (m, 2H), 7.17 (d, 2H), 7.25 (d, 2H), 7.34 (m, 1H).

(iii) Ethyl (2S)-3-(4-{2-[(2,4-difluorobenzyl)(4-ethylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (1.48 g, 5.0 mmol) and *N*-(2,4-difluorobenzyl)-*N*-(4-ethylbenzyl)amine (1.57 g, 6.0 mmol) in methylene chloride (50 mL) at 0 °C were added *N,N*-diisopropylethylamine (2.0 mL, 11.5 mmol) followed by *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.93 g, 6.0 mmol) and the reaction mixture was stirred overnight and then concentrated *in vacuo*. The residue was taken up in ethyl acetate (200 mL) and the organic phase was washed with 5% HCl (3 x 100 mL), saturated aqueous NaHCO<sub>3</sub> (100 mL), and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on silica gel (240 g) with methanol (0–4% gradient) in methylene chloride as the eluent and collection of pure fractions afforded 1.18 g (44%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.16 (t, 3H), 1.19–1.27 (m, 6H), 2.57–2.70 (m, 2H), 2.90–3.00 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.96 (m, 1H), 4.16 (q, 2H), 4.52, 4.54, 4.56 and 4.59 (4s, 4H, rotamers), 4.74 and 4.80 (2s, 2H, rotamers), 6.69–6.88 (m, 4H), 7.02–7.22 and 7.25–7.36 (2m, 7H, rotamers).

(iv) (2S)-3-(4-{2-[(2,4-Difluorobenzyl)(4-ethylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2S)-3-(4-{2-[(2,4-difluorobenzyl)(4-ethylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (1.13 g, 2.1 mmol) in acetonitrile (100 mL) was added aqueous 0.10 M LiOH (52 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 1.01 g (94%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.16 (t, 3H), 1.19–1.28 (m, 3H), 2.56–2.71 (m, 2H), 2.95 (m, 1H), 3.05 (m, 1H), 3.41 (m, 1H), 3.61 (m, 1H), 4.02 (m, 1H), 4.52, 4.54, 4.55 and 4.59 (4s,

4H, rotamers), 4.75 and 4.81 (2s, 2H, rotamers), 6.70–6.88 (m, 4H), 7.04–7.22 and 7.25–7.35 (2m, 7H, rotamers), 8.04 (bs, 1H).

#### Example 4

##### 5 (2S)-3-(4-{2-[Benzyl(methyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

##### (i) Ethyl (2S)-3-(4-{2-[benzyl(methyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.320 g, 1.08 mmol) in methylene chloride (10 mL) were added N-methylbenzylamine (0.145 g, 1.20 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.353 g, 1.10 mmol) and the reaction mixture was stirred at room temperature for three days. The resulting solution was diluted with methylene chloride (100 mL) and the organic phase was washed with 5% HCl (3 x 50 mL), aqueous NaHCO<sub>3</sub> (50 mL) and brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute<sup>®</sup> SPE Column, 10 g Si/70 mL) with methanol (0–1% gradient) in methylene chloride as the eluent afforded 0.186 g (43%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.10–1.24 (m, 6H), 2.88–2.99 (m, 2H), 2.91 and 2.95 (2s, 3H, rotamers), 3.33 (m, 1H), 3.58 (m, 1H), 3.95 (m, 1H), 4.08–4.20 (m, 2H), 4.57 and 4.59 (2s, 2H, rotamers), 4.69 and 4.70 (2s, 2H, rotamers), 6.77 and 6.87 (2d, 2H, rotamers), 7.07–7.38 (m, 7H).

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##### (ii) (2S)-3-(4-{2-[Benzyl(methyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2S)-3-(4-{2-[benzyl(methyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.155 g, 0.39 mmol) in THF (20 mL) was added aqueous 0.10 M LiOH (10 mL) and the reaction mixture was stirred overnight. After acidification with 5% HCl, the mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic phase was washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.139 g (97%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.10–1.20 (m, 3H), 2.86–3.10 (m, 2H), 2.94 and 2.97 (2s, 3H, rotamers), 3.38 (m, 1H), 3.61 (m, 1H), 4.01 (m, 1H), 4.59 and 4.61 (2s, 2H, rotamers), 4.72 and 4.73 (2s, 2H, rotamers), 6.78 and 6.87 (2d, 2H, rotamers), 7.10–7.40 (m, 7H), 8.97 (bs, 1H).

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Example 5(2S)-2-Ethoxy-3-[4-(2-{heptyl[(1-methylindol-2-yl)methyl]amino}-2-oxoethoxy)phenyl]propanoic acid(i) N-heptyl-N-[(1-methylindol-2-yl)methyl]amine

5 To a solution of 1-methylindole-2-carbaldehyde (1.59 g, 10.0 mmol) and heptylamine (1.49 mL, 10.0 mmol) in ethanol (50 mL) were added acetic acid (2.3 mL, 40 mmol) and sodium cyanoborohydride (0.75 g, 12.0 mmol) and the reaction mixture was stirred at room temperature overnight. Water (5 mL) was added and the mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (75 mL) and aqueous 1 M KOH (75 mL) and the

10 phases were separated. The aqueous layer was extracted with ethyl acetate (2 x 75 mL) and the combined organic phase was washed with brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a column of silica gel (130 g) with ethyl acetate (17–33% gradient) in heptane as the eluent yielded 1.57 g (61%) of a yellow oil, which solidified upon standing.

15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.87–0.95 (m, 3H), 1.20–1.40 (m, 8H), 1.46–1.60 (m, 2H), 2.70 (t, 3H), 3.78 (s, 3H), 3.94 (s, 2H), 6.39 (s, 1H), 7.09 (m, 1H), 7.20 (m, 1H), 7.31 (d, 1H), 7.58 (d, 1H).

(ii) Ethyl (2S)-2-ethoxy-3-[4-(2-{heptyl[(1-methylindol-2-yl)methyl]amino}-2-oxoethoxy)phenyl]propanoate

20 To a solution of {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.889 g, 3.00 mmol) and N-heptyl-N-[(1-methylindol-2-yl)methyl]amine (0.814 g, 3.15 mmol) in methylene chloride (30 mL) were added DMAP (0.403 g, 3.30 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.633 g, 3.30 mmol) and the reaction

25 mixture was stirred at room temperature for three days. The mixture was diluted with methylene chloride (100 mL) and the organic phase was washed with 2 M HCl (3 x 100 mL), saturated aqueous NaHCO<sub>3</sub> (100 mL), and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a column of silica gel (100 g) with methanol (0–5% gradient) in methylene chloride as the eluent yielded 0.71 g (43%) of a pale yellow oil.

30 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.82–0.93 (m, 3H), 1.18 (t, 3H), 1.14–1.36 (m, 11H), 1.47–1.62 (m, 2H), 2.91–3.03 (m, 2H), 3.20–3.29 and 3.30–3.47 (2m, 3H, rotamers), 3.58 (s, 3H),

3.61 (m, 1H), 3.98 (m, 1H), 4.18 (q, 2H), 4.73 (s, 2H), 4.86 (s, 2H), 6.44 (s, 1H), 6.87 (d, 2H), 7.06–7.34 (m, 5H), 7.57 (d, 1H).

(iii) (2S)-2-Ethoxy-3-[4-(2-{heptyl[(1-methylindol-2-yl)methyl]amino}-2-oxoethoxy)phenyl]propanoic acid

To a solution of ethyl (2S)-2-ethoxy-3-[4-(2-{heptyl[(1-methylindol-2-yl)methyl]amino}-2-oxoethoxy)phenyl]propanoate (0.655 g, 1.22 mmol) in THF (60 mL) was added aqueous 0.10 M LiOH (30 mL) and the reaction mixture was stirred at room temperature overnight. After acidification with 2 M HCl, the mixture was extracted with ethyl acetate (3 x 75 mL) and the combined organic phase was washed with brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.61 g (95%) of a pale yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.80–0.93 (m, 3H), 1.13–1.34 (m, 11H), 1.46–1.62 (m, 2H), 2.97 and 3.10 (AB part of ABX system, 2H), 3.19–3.29 and 3.38–3.55 (2m, 3H, rotamers), 3.58 (s, 3H), 3.59 (m, 1H), 4.07 (m, 1H), 4.73 (s, 2H), 4.86 (s, 2H), 6.43 (s, 1H), 6.88 (d, 2H), 7.05–7.33 (m, 5H), 7.56 (d, 1H).

Example 6

(2S)-3-(4-{2-[(2,3-Dimethoxybenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

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(i) N-Heptyl-2,3-dimethoxybenzamide

To a solution of 2,3-dimethoxybenzoic acid (4.55 g, 25.0 mmol) in methylene chloride (250 mL) were added heptylamine (2.78 g, 27.5 mmol) and DMAP (3.36 g, 27.5 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.27 g, 27.5 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was washed with 5% HCl (3 x 100 mL), saturated aqueous NaHCO<sub>3</sub> (100 mL), and brine (100 mL) and dried over MgSO<sub>4</sub>. Concentration *in vacuo* afforded 6.81 g (98%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.82–0.91 (m, 3H), 1.20–1.43 (m, 8H), 1.53–1.66 (m, 2H), 3.40–3.48 (m, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 7.02 (dd, 1H), 7.13 (t, 1H), 7.67 (dd, 1H), 7.93 (bs, 1H).

(ii) *N*-(2,3-Dimethoxybenzyl)-*N*-heptylamine

*N*-Heptyl-2,3-dimethoxybenzamide (6.47 g, 23.2 mmol) was dissolved in freshly distilled THF (230 mL) and cooled in an ice bath under an argon atmosphere. Borane (29 mL of a 2 M solution of the dimethylsulfide complex in diethyl ether) was added and the ice bath was removed after 15 minutes. The reaction mixture was refluxed overnight and was then allowed to cool to room temperature. The reaction was quenched by careful addition of 10% HCl (11 mL) and the mixture was stirred for four hours and then concentrated *in vacuo*. The residue was taken up in ethyl acetate (300 mL) and washed with aqueous 2 M K<sub>2</sub>CO<sub>3</sub> (3 x 100 mL) and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on silica gel (160 g) with ethyl acetate (33–100% gradient) in heptane and finally 5% ethanol in ethyl acetate as the eluent yielded 3.40 g (55%) of a light yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.83–0.91 (m, 3H), 1.20–1.35 (m, 8H), 1.42–1.54 (m, 2H), 2.54–2.61 (m, 2H), 3.79 (s, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.83 (d, 1H), 6.88 (d, 1H), 7.01 (t, 1H).

(iii) Ethyl (2*S*)-3-(4-{2-[(2,3-dimethoxybenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of *N*-(2,3-dimethoxybenzyl)-*N*-heptylamine (1.46 g, 5.5 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (1.48 g, 5.0 mmol) in methylene chloride (50 mL) at 0 °C were added *N,N*-diisopropylethylamine (2.0 mL, 11.5 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.93 g, 6.0 mmol) and the reaction mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The residue was taken up in ethyl acetate (200 mL) and the organic phase was washed with saturated aqueous NaHCO<sub>3</sub> (3 x 100 mL), 5% HCl (3 x 100 mL), and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on silica gel (100 g) with methanol (0–2% gradient) in methylene chloride as the eluent and collection of pure fractions yielded 1.57 g (58%) of a pale yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.82–0.90 (m, 3H), 1.11–1.30 (m, 14H), 1.46–1.64 (m, 2H), 2.89–2.98 (m, 2H), 3.20–3.28 and 3.28–3.40 (2m, 3H, rotamers), 3.59 (m, 1H), 3.81, 3.82, 3.85 and 3.87 (4s, 6H, rotamers), 3.95 (m, 1H), 4.11–4.20 (m, 2H), 4.59, 4.69, 4.70 and 4.72 (4s, 4H, rotamers), 6.69–6.91 (m, 4H), 6.95 and 7.02 (2t, 1H, rotamers), 7.11 and 7.16 (2d, 2H, rotamers).

(iv) (2S)-3-(4-{2-[(2,3-Dimethoxybenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2S)-3-(4-{2-[(2,3-dimethoxybenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (1.40 g, 2.55 mmol) in acetonitrile (100 mL) was added aqueous 0.10 M LiOH (50 mL) and the reaction mixture was stirred at room temperature overnight. The solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 1.29 g (98%) of a pale yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.81–0.91 (m, 3H), 1.13–1.32 (m, 11H), 1.46–1.64 (m, 2H), 2.94 (m, 1H), 3.07 (m, 1H), 3.25 and 3.34 (2m, 2H, rotamers), 3.44 (m, 1H), 3.59 (m, 1H), 3.82 (s, 3H), 3.86 and 3.88 (2s, 3H, rotamers), 4.03 (m, 1H), 4.60, 4.70, 4.72 and 4.74 (4s, 4H, rotamers), 6.70–6.92 (m, 4H), 6.96 and 7.03 (2t, 1H, rotamers), 7.12 and 7.17 (2d, 2H, rotamers).

Example 7

(2S)-3-(4-{2-[Butyl(2,3-dimethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(i) N-Butyl-2,3-dimethoxybenzamide

To a solution of 2,3-dimethoxybenzoic acid (4.55 g, 25.0 mmol) in methylene chloride (250 mL) were added butylamine (2.01 g, 27.5 mmol) and DMAP (3.36 g, 27.5 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.27 g, 27.5 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was washed with 5% HCl (3 x 100 mL), saturated aqueous NaHCO<sub>3</sub> (100 mL), and brine (100 mL) and dried over MgSO<sub>4</sub>. Concentration *in vacuo* afforded 5.59 g (94%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.94 (t, 3H), 1.35–1.47 (m, 2H), 1.53–1.63 (m, 2H), 3.40–3.48 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 7.00 (dd, 1H), 7.11 (t, 1H), 7.66 (dd, 1H), 7.92 (bs, 1H).

(ii) *N*-Butyl-*N*-(2,3-dimethoxybenzyl)amine

*N*-Butyl-2,3-dimethoxybenzamide (5.37 g, 22.6 mmol) was dissolved in freshly distilled THF (230 mL) and cooled in an ice bath under an argon atmosphere. Borane (28 mL of a 2 M solution of the dimethylsulfide complex in diethyl ether) was added and the ice bath was removed after 15 minutes. The reaction mixture was refluxed overnight and was then allowed to cool to room temperature. The reaction was quenched by careful addition of 10% HCl (11 mL) and the mixture was stirred for four hours and then concentrated *in vacuo*. The residue was taken up in ethyl acetate (300 mL) and washed with aqueous 2 M K<sub>2</sub>CO<sub>3</sub> (3 x 100 mL), and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on silica gel (160 g) with ethyl acetate (33–100% gradient) in heptane and finally 5% ethanol in ethyl acetate as the eluent yielded 2.74 g (54%) of a light yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.89 (t, 3H), 1.26–1.40 (m, 2H), 1.42–1.53 (m, 2H), 2.56–2.63 (m, 2H), 3.79 (s, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.83 (dd, 1H), 6.89 (dd, 1H), 7.01 (t, 1H).

(iii) Ethyl (2*S*)-3-(4-{2-[butyl(2,3-dimethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of *N*-butyl-*N*-(2,3-dimethoxybenzyl)amine (1.23 g, 5.5 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (1.48 g, 5.0 mmol) in methylene chloride (50 mL) at 0 °C were added *N,N*-diisopropylethylamine (2.0 mL, 11.5 mmol) followed by *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.93 g, 6.0 mmol) and the reaction mixture was stirred overnight and then concentrated *in vacuo*. The residue was taken up in ethyl acetate (200 mL) and the organic phase was washed with saturated aqueous NaHCO<sub>3</sub> (3 x 100 mL), 5% HCl (3 x 100 mL), and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on silica gel (120 g) with methanol (0–2% gradient) in methylene chloride as the eluent and collection of pure fractions afforded 1.07 g (43%) of a pale yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.84–0.94 (m, 3H), 1.12–1.19 (m, 3H), 1.19–1.35 (m, 5H), 1.46–1.64 (m, 2H), 2.88–3.00 (m, 2H), 3.21–3.29 and 3.29–3.40 (2m, 3H, rotamers), 3.59 (m, 1H), 3.82, 3.82, 3.86 and 3.88 (4s, 6H, rotamers), 3.96 (m, 1H), 4.11–4.21 (m, 2H), 4.60, 4.70, 4.71 and 4.73 (4s, 4H, rotamers), 6.69–6.92 (m, 4H), 6.96 and 7.03 (2t, 1H, rotamers), 7.12 and 7.16 (2d, 2H, rotamers).



(iv) (2S)-3-(4-{2-[Butyl(2,3-dimethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2S)-3-(4-{2-[(2,3-dimethoxybenzyl)(butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (1.02 g, 2.0 mmol) in acetonitrile (80 mL) was added aqueous 0.10 M LiOH (40 mL) and the reaction mixture was stirred at room temperature overnight. The solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.96 g (98%) of a light yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.84–0.94 (m, 3H), 1.12–1.20 (m, 3H), 1.20–1.36 (m, 2H), 1.45–1.64 (m, 2H), 2.94 (m, 1H), 3.06 (m, 1H), 3.26 and 3.35 (2m, 2H, rotamers), 3.43 (m, 1H), 3.59 (m, 1H), 3.82 and 3.82 (2s, 3H, rotamers), 3.86 and 3.88 (2s, 3H, rotamers), 4.03 (m, 1H), 4.60, 4.70, 4.72 and 4.74 (4s, 4H, rotamers), 6.70–6.92 (m, 4H), 6.96 and 7.03 (2t, 1H, rotamers), 7.12 and 7.17 (2d, 2H, rotamers).

Example 8

(2S)-3-(4-{2-[(4-Chlorobenzyl)(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(i) N-(4-Chlorobenzyl)-N-(4-isopropylbenzyl)amine

To a solution of 4-chlorobenzylamine (2.83 g, 20.0 mmol) and 4-isopropylbenzaldehyde (2.96 g, 20.0 mmol) in methanol (100 mL) were added acetic acid (4.6 mL, 80 mmol) and sodium cyanoborohydride (1.51 g, 24.0 mmol) and the solution was stirred at room temperature for three days. Water (5 mL) was added and the mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (100 mL) and aqueous 1 M KOH (100 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 100 mL) and the combined organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 5.80 g of crude product as a white semicrystalline oil. The product was used in the subsequent reaction step without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.22 (d, 6H), 2.88 (sep, 1H), 3.84 (s, 4H), 5.72 (bs, 1H), 7.22 (d, 2H), 7.28 (d, 2H), 7.31 (bs, 4H).

(ii) Ethyl (2*S*)-3-(4-{2-[(4-chlorobenzyl)(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of *N*-(4-chlorobenzyl)-*N*-(4-isopropylbenzyl)amine (1.64 g, 6.0 mmol) in methylene chloride (50 mL) at 0 °C were added {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (1.48 g, 5.0 mmol) and *N,N*-diisopropylethylamine (2.0 mL, 11.5 mmol) followed by *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.93 g, 6.0 mmol) and the reaction mixture was stirred overnight. The mixture was diluted with methylene chloride (100 mL) and the organic phase was washed with 2 M HCl (3 x 75 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 75 mL, some emulsions), and brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Twice repeated purification on silica gel with methanol (0–5% gradient) in methylene chloride as the eluent and collection of pure fractions afforded 1.28 g (46%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.16 (t, 3H), 1.19–1.28 (m, 9H), 2.82–3.02 (m, 3H), 3.35 (m, 1H), 3.61 (m, 1H), 3.97 (m, 1H), 4.17 (q, 2H), 4.49, 4.50, 4.52 and 4.54 (4s, 4H, rotamers), 4.74 and 4.77 (2s, 2H, rotamers), 6.75–6.86 (m, 2H), 7.04–7.36 (m, 10H).

(iii) (2*S*)-3-(4-{2-[(4-Chlorobenzyl)(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-(4-{2-[(4-chlorobenzyl)(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (1.15 g, 2.1 mmol) in acetonitrile (100 mL) was added aqueous 0.10 M LiOH (52 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 1.02 g (93%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.17 (t, 3H), 1.21–1.28 (m, 6H), 2.92 (m, 1H), 2.95 and 3.07 (AB part of ABX system, 2H), 3.44 (m, 1H), 3.61 (m, 1H), 4.04 (m, 1H), 4.49, 4.50, 4.53 and 4.55 (4s, 4H, rotamers), 4.75 and 4.78 (2s, 2H, rotamers), 6.76–6.87 (m, 2H), 7.04–7.36 (m, 10H).

Example 9(2S)-3-(4-{2-[(Cyclohexylmethyl)(2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid(i) *N*-(Cyclohexylmethyl)-*N*-(2,4-difluorobenzyl)amine

5 To a solution of 2,4-difluorobenzylamine (2.84 g, 20.0 mmol) and cyclohexanecarbaldehyde (2.60 mL, 20.0 mmol) in methanol (100 mL) were added acetic acid (4.6 mL, 80 mmol) and sodium cyanoborohydride (1.51 g, 24.0 mmol) and the solution was stirred at room temperature for three days. Water (10 mL) was added and the mixture was concentrated *in vacuo*. The residue was diluted with aqueous 1 M KOH (125 mL) and ethyl acetate (100 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 100 mL) and the combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute<sup>®</sup> SPE Column, 50 g Si/150 mL) with ethyl acetate (33–100% gradient) in heptane as the eluent yielded 2.40 g (50%) of white solids.

15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.90–1.04 (m, 2H), 1.07–1.34 (m, 3H), 1.61–1.85 (m, 6H), 2.72 (d, 2H), 4.19 (s, 2H), 6.90 (m, 1H), 6.97 (m, 1H), 7.0 (bs, 1H), 7.63 (m, 1H).

(ii) Ethyl (2S)-3-(4-{2-[(cyclohexylmethyl)(2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

20 To a solution of *N*-(cyclohexylmethyl)-*N*-(2,4-difluorobenzyl)amine (0.574 g, 2.00 mmol) and {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.593 g, 2.00 mmol) in methylene chloride (20 mL) were added *N,N*-diisopropylethylamine (0.80 mL, 4.6 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.674 g, 2.10 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was diluted with methylene chloride (100 mL) and the organic phase was washed with 2 M HCl (3 x 75 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 75 mL), and brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute<sup>®</sup> SPE Column, 20 g/70 mL) with methanol (0–2% gradient) in methylene chloride as the eluent yielded 0.59 g (57%) of a colourless oil.

30 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.83–1.02 (m, 2H), 1.08–1.30 (m, 9H), 1.51–1.82 (m, 6H), 2.88–3.00 (m, 2H), 3.10–3.22 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.96 (m, 1H), 4.16 (q,

2H), 4.63 (s, 2H), 4.70 and 4.71 (2s, 2H, rotamers), 6.72–6.90 (m, 4H), 7.05–7.18 and 7.18–7.29 (2m, 3H, rotamers).

(iii) (2*S*)-3-(4-{2-[(Cyclohexylmethyl)(2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-(4-{2-[(cyclohexylmethyl)(2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.297 g, 0.57 mmol) in acetonitrile (28 mL) was added aqueous 0.10 M LiOH (14 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.258 g (89%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.80–1.00 (m, 2H), 1.03–1.30 (m, 6H), 1.48–1.80 (m, 6H), 2.92 (m, 1H), 3.01 (m, 1H), 3.10–3.20 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.99 (m, 1H), 4.62 (s, 2H), 4.72 (s, 2H), 6.70–6.88 (m, 4H), 7.05–7.19 and 7.19–7.29 (2m, 3H, rotamers).

Example 10

(2*S*)-2-Ethoxy-3-(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(i) Ethyl (2*S*)-2-ethoxy-3-(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethoxy}phenyl)propanoate

To a solution of *N*-ethyl-*N*-(2-fluorobenzyl)amine (0.843 g, 5.50 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (1.482 g, 5.00 mmol) in methylene chloride (50 mL) were added *N,N*-diisopropylethylamine (2.00 mL, 11.5 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.93 g, 6.0 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (50 mL) and the organic phase was washed with 2 M HCl (3 x 75 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 75 mL), and brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute<sup>®</sup> SPE Column, 70 g/150 mL) with methanol (0–2% gradient) in methylene chloride as the eluent yielded 1.90 g (88%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.04–1.26 (m, 9H), 2.89–2.98 (m, 2H), 3.27–3.44 (m, 3H), 3.59 (m, 1H), 3.95 (m, 1H), 4.10–4.20 (m, 2H), 4.64, 4.67, 4.70, and 4.72 (4s, 4H, rotamers), 6.76 and 6.87 (2d, 2H, rotamers), 6.97–7.32 (m, 6H).

5

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 12.4, 13.9, 14.3, 15.1, 38.5, 41.0, 41.3 (d), 41.7, 44.3 (d), 60.9, 66.3, 67.6, 67.9, 80.4, 114.5, 114.6, 115.3 (d), 115.7 (d), 123.8 (d), 124.2 (d), 124.5 (m), 128.7, 128.7 129.1 (d), 129.5 (d), 130.3–130.6 (m), 130.5, 130.6, 156.8, 156.9, 160.9 (d), 161.1 (d), 168.0, 168.1, 172.6. (The number of peaks is larger than the number of carbon  
10 atoms due to rotamers.)

(ii) (2S)-2-Ethoxy-3-(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid

To a solution of ethyl (2S)-2-ethoxy-3-(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethoxy}phenyl)propanoate (0.980 g, 2.27 mmol) in acetonitrile (120 mL) was added aqueous 0.10 M  
15 LiOH (57 mL) and the reaction mixture was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.868 g (95%) of a pale yellow oil.

20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.05–1.28 (m, 6H), 2.87–2.99 (m, 1H), 2.99–3.10 (m, 1H), 3.33–3.45 (m, 3H), 3.61 (m, 1H), 4.01 (m, 1H), 4.65, 4.68, 4.72, and 4.73 (4s, 4H, rotamers), 6.77 and 6.87 (2d, 2H, rotamers), 6.96–7.33 (m, 6H), 9.04 (bs, 1H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 12.4, 13.9, 15.1, 38.0, 41.2, 41.4 (d), 41.7, 44.4 (d), 66.7,  
25 67.4, 67.7, 79.8, 114.6, 114.7, 115.3 (d), 115.7 (d), 123.6 (d), 124.0 (d), 124.5 (m), 128.7, 129.2 (d), 129.6 (d), 130.0–130.8 (m), 130.6, 130.7, 156.8, 156.9, 160.9 (d), 161.1 (d), 168.4, 168.5, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

Example 11

(2S)-3-(4-{2-[4-(benzyloxy)benzyl](butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(i) Ethyl (2S)-3-(4-{2-[4-(benzyloxy)benzyl](butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of *N*-[4-(benzyloxy)benzyl]-*N*-butylamine (3.59 g, 12.0 mmol) and {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (2.96 g, 10.0 mmol) in methylene chloride (100 mL) were added *N,N*-diisopropylethylamine (4.00 mL, 23.0 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (3.85 g, 12.0 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (100 mL) and the organic phase was washed with 5% HCl (3 x 75 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 75 mL), and brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute<sup>®</sup> SPE Column, 70 g/150 mL) with methanol (0–1% gradient) in methylene chloride as the eluent and collection of pure fractions yielded 1.80 g (33%) of a whitish oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.80–0.95 (m, 3H), 1.12–1.20 (m, 3H), 1.20–1.35 (m, 5H), 1.44–1.61 (m, 2H), 2.88–3.02 (m, 2H), 3.19–3.28 and 3.29–3.41 (2m, 3H, rotamers), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.54 and 4.55 (2s, 2H, rotamers), 4.66 and 4.72 (2s, 2H, rotamers), 5.50 and 5.06 (2s, 2H, rotamers), 6.76–7.00 (m, 4H), 7.07–7.21 (m, 4H), 7.28–7.47 (m, 5H).

(ii) (2S)-3-(4-{2-[4-(benzyloxy)benzyl](butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2S)-3-(4-{2-[4-(benzyloxy)benzyl](butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.116 g, 0.21 mmol) in acetonitrile (10 mL) was added aqueous 0.10 M LiOH (5 mL) and the reaction mixture was stirred at room temperature overnight. The solvent volume was reduced *in vacuo* and the remaining aqueous phase was diluted with water and aqueous 1 M KOH and washed with diethyl ether (2 x 50 mL). The aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.070 g (63%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.83–0.95 (m, 3H), 1.10–1.20 (m, 3H), 1.20–1.36 (m, 2H), 1.42–1.62 (m, 2H), 2.95 (m, 1H), 3.05 (m, 1H), 3.19–3.29 and 3.30–3.46 (2m, 3H, rotamers), 3.61 (m, 1H), 4.02 (m, 1H), 4.54 and 4.56 (2s, 2H, rotamers), 4.68 and 4.74 (2s, 2H, rotamers), 5.04 and 5.06 (2s, 2H, rotamers), 6.76–7.00 (m, 4H), 7.09–7.22 (m, 4H), 7.28–7.47 (m, 5H).

### Example 12

#### (2S)-3-(4-{2-[bis(4-Chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(i) Ethyl (2S)-3-(4-{2-[bis(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate  
To a suspension of *N,N*-bis(4-chlorobenzyl)amine (0.958 g, 3.60 mmol) in methylene chloride (30 mL) were added {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.889 g, 3.00 mmol) and *N,N*-diisopropylethylamine (1.20 mL, 6.9 mmol) followed by *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.01 g, 3.15 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (220 mL) and the organic phase was washed with 2 M HCl (3 x 50 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 50 mL), and brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute<sup>®</sup> SPE Column, 50 g/150 mL) with methanol (0–2% gradient) in methylene chloride as the eluent yielded 1.02 g (62%) of an oil, which solidified upon standing to give white solids.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.17 (t, 3H), 1.23 (t, 3H), 2.90–3.00 (m, 2H), 3.36 (m, 1H), 3.61 (m, 1H), 3.97 (m, 1H), 4.17 (q, 2H), 4.50 (s, 2H), 4.76 (s, 4H), 6.80 (d, 2H), 7.03–7.11 (m, 4H), 7.15 (d, 2H), 7.21–7.35 (m, 4H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.4, 15.2, 38.5, 47.6, 49.2, 61.0, 66.3, 68.1, 80.3, 114.5, 128.5, 129.0, 129.3, 129.9, 130.7, 133.7, 133.9, 134.5, 135.0, 156.6, 168.7, 172.5.

(ii) (2S)-3-(4-{2-[bis(4-Chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid  
To a solution of ethyl (2S)-3-(4-{2-[bis(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.597 g, 1.10 mmol) in acetonitrile (54 mL) was added aqueous 0.10 M LiOH (27 mL) and the reaction mixture was stirred at room temperature overnight. The solvent volume was reduced *in vacuo* and the remaining aqueous phase was diluted with

water and aqueous 1 M KOH (to a total volume of 400 mL, pH~9) and washed with diethyl ether (2 x 100 mL). (The extraction process was complicated by the formation of emulsions.) The aqueous phase was acidified with 2 M HCl and extracted with ethyl acetate (4 x 75 mL). The combined organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.475 g (84%) of a whitish oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.19 (t, 3H), 2.97 and 3.08 (AB part of ABX system, 2H), 3.47 (m, 1H), 3.61 (m, 1H), 4.06 (m, 1H), 4.50 (s, 4H), 4.76 (s, 2H), 6.80 (d, 2H), 7.04–7.12 (m, 4H), 7.15 (d, 2H), 7.25 (d, 2H), 7.32 (d, 2H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 15.2, 37.7, 47.7, 49.3, 67.0, 68.0, 79.8, 114.7, 128.5, 129.0, 129.3, 129.9, 130.0, 130.9, 133.7, 133.9, 134.4, 135.0, 156.8, 168.8, 174.1.

### Example 13

(2S)-3-(4-{2-[(4-*tert*-Butylbenzyl)(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

#### (i) *N*-(4-*tert*-Butylbenzyl)-*N*-(4-chlorobenzyl)amine

To a solution of 4-*tert*-butylbenzaldehyde (3.24 g, 20.0 mmol) and 4-chlorobenzylamine (2.43 mL, 20.0 mmol) in methanol (100 mL) were added acetic acid (4.6 mL, 80 mmol) and sodium cyanoborohydride (1.51 g, 24.0 mmol) and the reaction mixture was stirred at room temperature overnight. Water (10 mL) was added and the mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (50 mL) and aqueous 1 M KOH (50 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute<sup>®</sup> SPE Column, 70 g/150 mL) with ethyl acetate (33–100% gradient) in heptane as the eluent yielded 4.31 g (75%) of white solids.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.28 (s, 9H), 3.90 (s, 2H), 3.92 (s, 2H), 6.15 (bs, 1H), 7.28–7.33 (m, 6H), 7.40 (d, 2H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 31.3, 34.8, 50.1, 50.8, 126.3, 129.0, 129.4, 129.5, 130.9, 131.2, 135.3, 152.6.



(ii) Ethyl (2*S*)-3-(4-{2-[(4-*tert*-butylbenzyl)(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.889 g, 3.00 mmol) in methylene chloride (30 mL) were added *N*-(4-*tert*-butylbenzyl)-*N*-(4-chlorobenzyl)amine (1.04 g, 3.60 mmol), *N,N*-diisopropylethylamine (1.20 mL, 6.9 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.01 g, 3.15 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (220 mL) and the organic phase was washed with 2 M HCl (3 x 50 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 50 mL), and brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Twice repeated purification on prepacked columns of silica gel (Isolute<sup>®</sup> SPE Column, 50 g/150 mL) with methanol (0–2% gradient) in methylene chloride as the eluent and collection of pure fractions yielded 0.459 g (27%) of a whitish oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.16 (t, 3H), 1.23 (t, 3H), 1.31 and 1.33 (2s, 9H, rotamers), 2.88–3.02 (m, 2H), 3.35 (m, 1H), 3.61 (m, 1H), 3.97 (m, 1H), 4.17 (q, 2H), 4.49 and 4.50 (2s, 2H, rotamers), 4.53 and 4.55 (2s, 2H, rotamers), 4.74 and 4.77 (2s, 2H, rotamers), 6.76–6.86 (m, 2H), 7.09 (d, 4H), 7.14 (d, 2H), 7.24, 7.31, and 7.37 (3d, 4H, rotamers).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.3, 15.2, 31.4, 34.7, 38.6, 47.8, 48.0, 49.1, 49.4, 60.9, 66.3, 67.7, 68.1, 80.4, 114.6, 114.6, 125.7, 126.0, 126.7, 128.3, 128.4, 128.8, 129.1, 129.9, 130.6, 130.6, 132.8, 133.4, 133.7, 134.8, 135.5, 150.8, 151.2, 156.7, 168.5, 168.6, 172.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

(iii) (2*S*)-3-(4-{2-[(4-*tert*-Butylbenzyl)(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-(4-{2-[(4-*tert*-butylbenzyl)(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.400 g, 0.71 mmol) in acetonitrile (36 mL) was added aqueous 0.10 M LiOH (18 mL) and the reaction mixture was stirred at room temperature overnight. After acidification with 2 M HCl, the solvent volume was reduced *in vacuo* and the mixture was extracted with ethyl acetate (3 x 75 mL). The combined organic phase was washed with brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.375 g (99%) of a whitish oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.18 (t, 3H), 1.31 and 1.33 (2s, 9H, rotamers), 2.96 and 3.07 (AB part of ABX system, 2H), 3.44 (m, 1H), 3.61 (m, 1H), 4.04 (m, 1H), 4.49 and 4.50 (2s, 2H, rotamers), 4.53 and 4.55 (2s, 2H, rotamers), 4.75 and 4.78 (2s, 2H, rotamers), 6.76–6.87 (m, 2H), 7.09 (d, 4H), 7.15 (d, 2H), 7.24, 7.31, and 7.37 (3d, 4H, rotamers).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 15.2, 31.5, 34.7, 37.9, 47.8, 48.0, 49.1, 49.5, 67.0, 67.6, 68.0, 79.8, 114.7, 114.8, 125.7, 126.1, 126.8, 128.3, 128.4, 128.9, 129.2, 129.9, 130.0, 130.8, 132.7, 133.4, 133.5, 133.7, 134.8, 135.4, 150.8, 151.2, 156.9, 168.6, 168.8, 174.7. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

#### Example 14

(2S)-3-[4-(2-((4-chlorobenzyl)[4-(trifluoromethyl)benzyl]amino)-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

(i) Ethyl (2S)-3-[4-(2-((4-chlorobenzyl)[4-(trifluoromethyl)benzyl]amino)-2-oxoethoxy)phenyl]-2-ethoxypropanoate

To a suspension of *N*-(4-chlorobenzyl)-*N*-[4-(trifluoromethyl)benzyl]amine (0.989 g, 3.30 mmol) and {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.889 g, 3.00 mmol) in methylene chloride (60 mL) were added *N,N*-diisopropylethylamine (1.20 mL, 6.9 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.01 g, 3.1 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (190 mL) and the organic phase was washed with 2 M HCl (3 x 50 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 50 mL), and brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Twice repeated purification on prepacked columns of silica gel (Isolute<sup>®</sup> SPE Column, 70 g/150 mL) with methanol (0–2% gradient) in methylene chloride as the eluent yielded 1.02 g (59%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.16 (t, 3H), 1.22 (t, 3H), 2.90–3.00 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.17 (q, 2H), 4.52 (s, 2H), 4.59 (s, 2H), 4.76 and 4.78 (2s, 2H, rotamers), 6.77 and 6.81 (2d, 2H, rotamers), 7.03–7.11 (m, 2H), 7.11–7.19 (m, 2H), 7.20–7.36 (m, 4H), 7.53 and 7.60 (2d, 2H rotamers).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.4, 15.2, 38.5, 47.8, 47.9, 49.5, 61.0, 66.3, 68.1, 68.2, 80.3, 114.5, 114.5, 125.7 (m), 126.0 (m), 127.4, 128.5, 128.6, 129.0, 129.3, 129.6–131.2 (m), 129.9, 130.8, 130.8, 133.8, 134.0, 134.3, 134.9, 140.2, 140.6, 156.5, 168.8, 172.5. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon not reported)

(ii) (2S)-3-[4-(2-{(4-Chlorobenzyl)[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

To a solution of ethyl (2S)-3-[4-(2-{(4-chlorobenzyl)[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoate (0.482 g, 0.83 mmol) in acetonitrile (42 mL) was added aqueous 0.10 M LiOH (21 mL) and the solution was stirred at room temperature overnight. After acidification with 2 M HCl, the solvent volume was reduced *in vacuo* and the mixture was extracted with ethyl acetate (3 x 75 mL). The combined organic phase was washed with brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.407 g (89%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.18 (t, 3H), 2.97 and 3.07 (AB part of ABX system, 2H), 3.44 (m, 1H), 3.62 (m, 1H), 4.04 (m, 1H), 4.53 (s, 2H), 4.60 (s, 2H), 4.77 and 4.79 (2s, 2H, rotamers), 6.77 and 6.81 (2d, 2H, rotamers), 7.04–7.12 (m, 2H), 7.12–7.20 (m, 2H), 7.21–7.37 (m, 4H), 7.53 and 7.60 (2d, 2H, rotamers).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 15.2, 37.9, 47.9, 48.0, 49.6, 66.9, 68.0, 68.1, 79.7, 114.6, 114.6, 125.7 (m), 126.0 (m), 127.3, 128.5, 128.6, 129.0, 129.3, 129.9, 130.2, 130.9, 133.8, 134.0, 134.2, 134.8, 140.1, 140.5, 156.6, 169.0, 175.2. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon and quarternary carbon α to the trifluoromethyl group not reported.)

#### Example 15

(2S)-3-[4-(2-{bis[4-(Trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

(i) Ethyl (2S)-3-[4-(2-{bis[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoate

To a solution of *N,N*-bis[4-(trifluoromethyl)benzyl]amine (0.733 g, 2.20 mmol) and {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.593 g, 2.00 mmol) in methylene chloride

(20 mL) were added *N,N*-diisopropylethylamine (0.80 mL, 4.6 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.674 g, 2.10 mmol) and the reaction mixture was stirred at room temperature for 4 h. The resulting solution was diluted with methylene chloride (130 mL) and the organic phase was washed with 5% HCl (3 x 75 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 75 mL), and brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 70 g/150 mL) with methanol (0–1% gradient) in methylene chloride as the eluent yielded 0.91 g (74%) of a whitish oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.15 (t, 3H), 1.22 (t, 3H), 2.90–3.00 (m, 1H), 3.35 (m, 1H), 3.60 (m, 1H), 3.96 (m, 1H), 4.16 (q, 2H), 4.61 (s, 2H), 4.63 (s, 2H), 4.79 (s, 2H), 6.78 (d, 2H), 7.15 (d, 2H), 7.26 (m, 2H), 7.53 (d, 2H), 7.60 (d, 2H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.3, 15.2, 38.5, 48.2, 49.8, 60.9, 66.3, 68.2, 80.3, 114.5, 125.8 (m), 126.1 (m), 127.4, 128.6, 130.1 (q), 130.8, 130.9, 140.1, 140.5, 156.5, 169.0, 172.5. (Trifluorinated carbon not reported.)

(ii) (2*S*)-3-[4-(2-{bis[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-[4-(2-{bis[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoate (0.662 g, 1.1 mmol) in acetonitrile (54 mL) was added aqueous 0.10 M LiOH (27 mL) and the solution was stirred at room temperature overnight. The solvent volume was reduced *in vacuo* and the remaining aqueous phase was diluted with water and aqueous 0.10 M LiOH (to a total volume of 300 mL, pH~12) and washed with diethyl ether (2 x 100 mL). (The extraction process was complicated by the formation of emulsions.) The aqueous phase was acidified with 2 M HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford 0.292 g (46%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.18 (t, 3H), 2.97 and 3.07 (AB part of ABX system, 2H), 3.46 (m, 1H), 3.62 (m, 1H), 4.05 (dd, 1H), 4.62 (s, 2H), 4.64 (s, 2H), 4.80 (s, 2H), 6.79 (d, 2H), 7.16 (d, 2H), 7.22–7.31 (m, 4H), 7.53 (d, 2H), 7.60 (d, 2H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  15.2, 37.8, 48.3, 49.9, 66.9, 68.1, 79.7, 114.6, 125.8 (m), 126.1 (m), 127.4, 128.6, 130.5 (q), 130.2, 130.9, 140.0, 140.4, 156.6, 169.1, 174.9. (Trifluorinated carbon not reported.)

5 Example 16

(2S)-3-(4-{2-[Benzyl(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(i) Ethyl (2S)-3-(4-{2-[benzyl(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.296 g, 1.00 mmol) and *N*-benzyl-*N*-ethylamine (0.149 g, 1.10 mmol) in methylene chloride (10 mL) were added *N,N*-diisopropylethylamine (0.40 mL, 2.3 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.353 g, 1.10 mmol) and the reaction mixture was stirred at room temperature for three days. The resulting solution was diluted with methylene chloride (90 mL) and the organic phase was washed with 2 M HCl (3 x 50 mL), saturated aqueous  $\text{NaHCO}_3$  (2 x 50 mL), and brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute<sup>®</sup> SPE Column, 70 g/150 mL) with methanol (0–1% gradient) in methylene chloride as the eluent and collection of pure fractions yielded 0.129 g (31%) of a whitish oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.06–1.32 (m, 9H), 2.87–3.02 (m, 2H), 3.26–3.48 (m, 3H), 3.60 (m, 1H), 3.96 (m, 1H), 4.10–4.21 (m, 2H), 4.61 and 4.62 (2s, 2H, rotamers), 4.66 and 4.74 (2s, 2H, rotamers), 6.78 and 6.89 (2d, 2H, rotamers), 7.08–7.40 (m, 7H).

(ii) (2S)-3-(4-{2-[Benzyl(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2S)-3-(4-{2-[benzyl(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.112 g, 0.27 mmol) in acetonitrile (14 mL) was added aqueous 0.10 M LiOH (7 mL) and the reaction mixture was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to afford 0.096 g (92%) of a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.05–1.21 (m, 6H), 2.85–3.10 (m, 2H), 3.28–3.48 (m, 3H), 3.61 (m, 1H), 4.01 (m, 1H), 4.61 and 4.62 (2s, 2H, rotamers), 4.67 and 4.75 (2s, 2H, rotamers), 6.76 and 6.88 (2d, 2H, rotamers), 7.08–7.38 (m, 7H), 8.78 (bs, 1H).

5 Example 17

(2S)-3-(4-{2-[(4-*tert*-Butylbenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

10 (i) Ethyl (2S)-3-(4-{2-[(4-*tert*-butylbenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of *N*-(4-*tert*-butylbenzyl)-*N*-ethylamine (0.383 g, 2.00 mmol) and {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.593 g, 2.00 mmol) in methylene chloride (20 mL) were added *N,N*-diisopropylethylamine (0.80 mL, 4.6 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.706 g, 2.20 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (40 mL) and the organic phase was washed with 5% HCl (50 mL), saturated aqueous NaHCO<sub>3</sub> (50 mL), and brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 50 g/150 mL) with methylene chloride/ethyl acetate 10:1 as the eluent yielded 0.54 g (58%) of a colourless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.07–1.25 (m, 9H), 1.30 and 1.32 (2s, 9H, rotamers), 2.88–3.00 (m, 2H), 3.28–3.40 and 3.40–3.48 (2m, 3H, rotamers), 3.60 (m, 1H), 3.96 (m, 1H), 4.12–4.20 (m, 2H), 4.57 and 4.59 (2s, 2H, rotamers), 4.66 and 4.73 (2s, 2H, rotamers), 6.78 and 6.89 (2d, 2H, rotamers), 7.09–7.20 (m, 4H), 7.31 and 7.36 (2d, 2H, rotamers).

25

(ii) (2S)-3-(4-{2-[(4-*tert*-Butylbenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2S)-3-(4-{2-[(4-*tert*-butylbenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.520 g, 1.11 mmol) in THF (50 mL) was added aqueous 0.10 M LiOH (25 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (2 x 50 mL). The combined organic

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phase was washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afforded 0.42 g (86%) of a colourless oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.08–1.22 (m, 6H), 1.30 and 1.32 (2s, 9H, rotamers), 2.94 (m, 1H), 3.07 (m, 1H), 3.30–3.50 (m, 3H), 3.59 (m, 1H), 4.04 (m, 1H), 4.57 and 4.59 (2s, 2H, rotamers), 4.67 and 4.74 (2s, 2H, rotamers), 6.79 and 6.89 (2d, 2H, rotamers), 7.09–7.21 (m, 4H), 7.31 and 7.36 (2d, 2H, rotamers).

The following examples were prepared in a similar manner.

Example 18

(2*S*)-3-(4-{2-[(4-Cyclohexylbutyl) (2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid.

Example 19

(2*S*)-3-(4-{2-[(2,4-Difluorobenzyl)(4-biphenylethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid.

Example 20

(2*S*)-3-(4-{3-[(2,4-Difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)-2-ethoxypropanoic acid.

Example 21

(2*S*)-3-(4-{3-[(Cyclohexylmethyl)(hexyl)amino]-3-oxopropyl}phenyl)-2-ethoxypropanoic acid.

Example 22

(2*S*)-3-[4-(2-{(4-Chlorobenzyl)[2-methoxybenzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid.

Example 23

(2*S*)-3-(4-{2-[(butyl)(4-methanesulfonyloxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid.

were performed by plate chemistry.

The following compounds were prepared by one of the following methods.

### **Method A**

#### **Reductive Amination**

1.0 ml of amine solutions was added to 0.8 ml of aldehyde solutions and the resulting mixtures were stirred for 12 h in sealed 4 ml glass vial.

Then ca. 300 mg of borohydride resin (Aldrich 2.5 mmol/g loading) was manually added to the individual vials, and the mixture was stirred for 8 - 12 h (no seal, H<sub>2</sub>-evolution; after 5 h add additional 1.0 ml of MeOH).

The mixture was filtered through a filter plate and washed once with 2.0 ml of MeOH. The filtrates were collected in 24-well plates with 4 ml glass vials. Then the solvent was removed in vacuo, using the HT-4 vacuum centrifuge (30°C, 5h, vacramp).

To the residue was added polymer supported aldehyde resin (Novabiochem 2.85 mmol/g loading; 80-100 mg), to remove the excess of amine and 2 ml of dry THF. The resulting mixture was stirred at rt for 6-8 h, filtered through a filter plate, washed once with 1.0 ml of THF and the filtrate was collected in 24-well plates with 4 ml glass vials. Then the solvent was removed in vacuo, using the HT-4 vacuum centrifuge (30°C, 5h, vacramp).

### **Method B**

#### **Amide Formation** {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid

To the residues were added the acid chloride solution (2.0 ml) and PS-DIEA (Argonaut 3.83 mmol/g loading; 70-80 mg) and the resulting mixture is stirred for 5-12 h.

The solutions were filtered through NH<sub>2</sub>-plates (Isolute; 500 mg) to remove any excess of acid chloride and washed with 1.0 ml THF. The filtrates were collected in 24-well plates with 4 ml glass vials.

If the formed amide does not contain a tertiary amino group, the solutions are filtered through SCX-plates (Isolute; 1 g (SCX-2, PRS & SCX-3 can be used as well)) to remove the excess of secondary amine. The SCX columns are washed with 1.0 ml of THF. The combined filtrates were collected in 24-well plates with 4 ml glass vials.

If the formed amide does contain a tertiary amine group, polymer supported isocyanate (Novabiochem 1.5 mmol/g; ca 100 mg) was added and the mixture was stirred for



additional 6 h at RT. This is to remove any excess of secondary amine. Then the mixtures were filtered through filter plates into 24-well plates with 4 ml glass vials, followed by a wash of 1.0 ml THF. The filtrates were collected in 24-well plates with 4 ml glass vials. The solvent was removed in vacuum, using the HT-4 vacuum centrifuge (30°C, 5h, vacramp).

### Hydrolysis

The dry residues (esters) are dissolved in 1.2 ml of THF. 400 µl of the solution is transferred to a preweighed blue well plate. The daughter plate is analysed by LC-MS (purified by preparative HPLC if needed) and the solvent is removed in vacuum, using the HT-4 vacuum centrifuge (30°C, 5h, vacramp). The dry compounds (daughter plate) are then quantified by automatic weighing and submitted to screen.

The mother plate (containing esters dissolved in 0.8 ml THF) is treated with 0.8 ml 0.175M LiOH (per vial) overnight.

If a compound contains a tertiary amine, the solution is poured onto an SCX column (Isolute; 1 g (SCX-2, PRS & SCX-3 can be used as well)) to catch the product. The SCX columns are washed with 3 x 1.0 ml of THF/MeOH. Afterwards the product is eluted with 4.0 ml of MeOH, saturated with ammonia.

If a compound does not contain a tertiary amine, the solvent is removed in vacuum, using the HT-4 vacuum centrifuge (30°C, 12h, vacramp). The dry compounds are dissolved with 1.0ml 0.2M HCl, followed by addition of 2.0 ml of DCM. The mixtures are vigorously shaken for 30 min. Phase separators (6 ml, Whatman) are used to separate the DCM layer, which contains the product, from the water phase. The compounds are collected in 24-well plates with 4 ml glass vials. The solvent is removed in vacuum, using the HT-4 vacuum centrifuge (30°C, 5h, vacramp).

The dry compounds are dissolved with 0.5 ml THF (or appropriate solvent) and transferred to a preweighed blue-well plate. This is repeated with 0.3 ml MeOH. The solvent is afterwards removed in vacuum, using the HT-4 vacuum centrifuge (30°C, 5h, vacramp). The plate is analysed by LC-MS (purified by preparative HPLC if needed) and the dry compounds are then quantified by automatic weighing and submitted to screen.

The following compounds were prepared by these methods:

(2*S*)-3-(4-{2-[benzyl(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

5 (2*S*)-2-ethoxy-3-(4-{2-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2*S*)-3-(4-{2-[butyl(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

10 (2*S*)-3-(4-{2-[(2-chlorobenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2*S*)-2-ethoxy-3-(4-{2-[heptyl(4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2*S*)-3-(4-{2-[[4-(4-cyanocyclohexyl)methyl](4-isopropylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

15 (2*S*)-2-ethoxy-3-(4-{2-[(4-isopropylbenzyl)(2-methoxybenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2*S*)-3-(4-{2-[(2-chlorobenzyl)(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

20 (2*S*)-3-(4-{2-[(4-chlorobenzyl)(2,3-dimethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2*S*)-3-(4-{2-[(1,3-benzodioxol-5-ylmethyl)(4-ethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2*S*)-3-(4-{2-[(1,3-benzodioxol-5-ylmethyl)(3-bromobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

25 (2*S*)-3-[4-(2-{(1,3-benzodioxol-5-ylmethyl)[3-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

(2*S*)-3-(4-{2-[(3,5-dimethoxybenzyl)(4-ethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

30 (2*S*)-3-(4-{2-[(3-chloro-4-fluorobenzyl)(4-ethoxybenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(2*S*)-2-ethoxy-3-(4-{2-[(4-ethoxybenzyl)(2-thienylmethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

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- (2S)-3-(4-{2-[benzyl(isopropyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2S)-3-{4-[2-(dibenzylamino)-2-oxoethoxy]phenyl}-2-ethoxypropanoic acid
- (2S)-3-(4-{2-[bis(2-methoxyethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 5 (2S)-2-ethoxy-3-[4-(2-{heptyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]propanoic acid
- (2S)-2-ethoxy-3-[4-(2-{heptyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]propanoic acid
- (2S)-2-ethoxy-3-(4-{2-[(4-ethylbenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- 10 (2S)-3-(4-{2-[(4-*tert*-butylbenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2S)-2-ethoxy-3-(4-{2-[heptyl(4-isobutylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- (2S)-3-(4-{2-[benzyl(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 15 (2S)-2-ethoxy-3-(4-{2-[(4-fluorobenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- (2S)-3-(4-{2-[(4-chlorobenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2S)-3-(4-{2-[(4-bromobenzyl)(heptyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 20 acid
- (2S)-3-(4-{2-[butyl(4-ethylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2S)-3-(4-{2-[butyl(4-*tert*-butylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2S)-3-(4-{2-[butyl(4-isobutylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 25 acid
- (2S)-3-(4-{2-[benzyl(butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2S)-3-(4-{2-[butyl(4-fluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2S)-3-(4-{2-[(4-bromobenzyl)(butyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 30 acid
- (2S)-3-(4-{2-[butyl(2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- acid

- (2*S*)-3-[4-(2-{(4-chlorobenzyl)[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(4-chlorobenzyl)(4-ethylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 5 (2*S*)-3-(4-{2-[(4-chlorobenzyl)(4-isobutylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(benzyl(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(4-chlorobenzyl)(4-fluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 10 (2*S*)-3-(4-{2-[(4-bromobenzyl)(4-chlorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-3-(4-{2-[(4-chlorobenzyl)(2,4-difluorobenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-ethoxy-3-[4-(2-{(4-methylbenzyl)[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]propanoic acid
- 15 (2*S*)-2-ethoxy-3-[4-(2-{(4-methylbenzyl)[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]propanoic acid
- (2*S*)-2-ethoxy-3-(4-{2-[(4-ethylbenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- 20 (2*S*)-3-(4-{2-[(4-*tert*-butylbenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- (2*S*)-2-ethoxy-3-(4-{2-[(4-isobutylbenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- (2*S*)-3-(4-{2-[(benzyl(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 25 acid
- (2*S*)-2-ethoxy-3-(4-{2-[(4-fluorobenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)propanoic acid
- (2*S*)-3-(4-{2-[(4-chlorobenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid
- 30 (2*S*)-3-(4-{2-[(4-bromobenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid and

(2S)-3-(4-{2-[(2,4-difluorobenzyl)(4-methylbenzyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid.

### BIOLOGICAL ACTIVITY

5 The compounds of the invention were tested in the assays described in WO 03/051821.

### ASSAY PROCEDURE

Stock solutions of compounds in DMSO were diluted in appropriate concentration ranges in master plates. From master plates, compounds were diluted in culture media to obtain  
10 test compound solutions for final doses.

After adjustment of the amount of cell medium to 75  $\mu$ l in each well, 50  $\mu$ l test compound solution was added. Transiently transfected cells were exposed to compounds for about 24 hours before the luciferase detection assay was performed. For luciferase assays, 100  $\mu$ l of  
15 assay reagent was added manually to each well and plates were left for approximately 20 minutes in order to allow lysis of the cells. After lysis, luciferase activity was measured in a 1420 Multiwell counter, Victor, from Wallach.

### Reference compounds

20 The TZD pioglitazone was used as reference substance for activation of both human and murine PPAR $\gamma$ . 5,8,11,14-Eicosatetrayonic acid (ETYA) was used as reference substance for human PPAR $\alpha$ .

### Calculations and analysis

25 For calculation of EC<sub>50</sub> values, a concentration-effect curve was established. Values used were derived from the average of two or three independent measurements (after subtraction of the background average value) and were expressed as the percentage of the maximal activation obtained by the reference compound. Values were plotted against the logarithm of the test compound concentration. EC<sub>50</sub> values were estimated by linear intercalation

between the data points and calculating the concentration required to achieve 50% of the maximal activation obtained by the reference compound.

5 The compounds of formula I have an  $EC_{50}$  of less than  $0.1\mu\text{mol/l}$  for  $PPAR\alpha$  and particular compounds have an  $EC_{50}$  of less than  $0.01\mu\text{mol/l}$ . Additionally in particular compounds the ratio of the  $EC_{50}$  ( $PPAR\gamma$ ) :  $EC_{50}$  ( $PPAR\alpha$ ) is greater than 150:1. It is believed that this ratio is important with respect to the pharmacological activity of the compounds and to their therapeutic profile.

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Example no	$EC_{50}$ $PPAR\alpha$ ( $\mu\text{M}$ )	ratio $EC_{50}$ ( $PPAR\gamma$ ): $EC_{50}$ ( $PPAR\alpha$ )
12	0.003	>1000
13	0.008	>400
15	0.003	>900

In addition the compounds of the present invention exhibit improved DMPK (Drug Metabolism and Pharmacokinetic) properties for example they exhibit improved metabolic stability *in vitro*. The compounds also have a promising toxicological profile.

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